(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 May 2003 (08.05.2003)

PCT

(10) International Publication Number
WO 03/037223 A1

(51) International Patent Classification[7]: A61F 2/06

(21) International Application Number: PCT/US02/34350

(22) International Filing Date: 25 October 2002 (25.10.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/002,595 1 November 2001 (01.11.2001) US
10/017,500 14 December 2001 (14.12.2001) US

(71) Applicant *(for all designated States except US)*: **AVANTEC VASCULAR CORPORATION** [US/US]; 1049 Kiel Street, Sunnyvale, CA 94089 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SIRHAN, Motasim** [US/US]; 794 West Knickerbocker Drive, Sunnyvale, CA 94087 (US). **YAN, John** [US/US]; 128 Anne Way, Los Gatos, CA 95032 (US).

(74) Agents: **BAINS, Nena** et al.; Townsend and Townsend and Crew LLP, Two Embarcadero Center, 8th Floor, San Francisco, CA 94111-3834 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

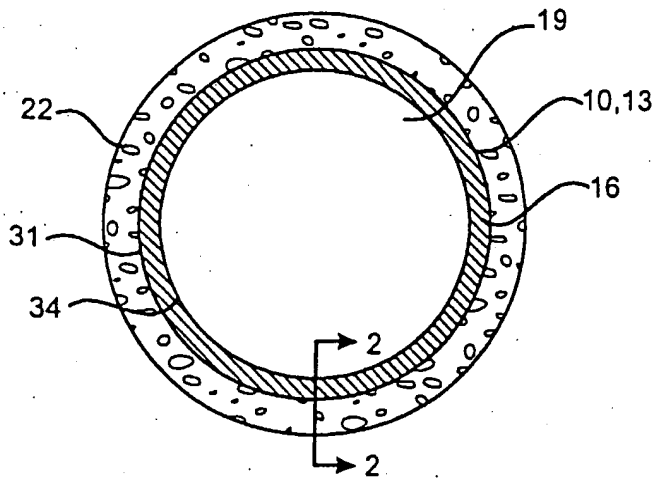
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: APPARATUS AND METHODS FOR VARIABLY CONTROLLED SUBSTANCE DELIVERY FROM IMPLANTED PROSTHESES



(57) Abstract: The present invention provides improved stents and other prostheses for delivering substances to vascular and other luminal and intracorporeal environments. In particular, the present invention provides luminal prostheses (13) which allow for programmed and controlled substance delivery protocols for a variety of purposes. The prostheses (13) comprised a scaffold which is implanted within the body lumen and a substance reservoir present over at least a portion of the scaffold. Usually, a rate-controlling element will be formed over the substance-containing reservoir to provide for a number of different substance release characteristics.

WO 03/037223 A1

the result of injury to the blood vessel wall during the lumen opening angioplasty procedure. In some patients, the injury initiates a repair response that is characterized by smooth muscle cell proliferation referred to as "hyperplasia" in the region traumatized by the angioplasty. This proliferation of smooth muscle cells re-narrows the lumen that was opened by the angioplasty within a few weeks to a few months, thereby necessitating a repeat PTA or other procedure to alleviate the restenosis.

[06] A number of strategies have been proposed to treat hyperplasia and reduce restenosis. Previously proposed strategies include prolonged balloon inflation during angioplasty, treatment of the blood vessel with a heated balloon, treatment of the blood vessel with radiation following angioplasty, stenting of the region, and other procedures. While these proposals have enjoyed varying levels of success, no one of these procedures is proven to be entirely successful in substantially or completely avoiding all occurrences of restenosis and hyperplasia.

[07] As an alternative or adjunctive to the above mentioned therapies, the administration of therapeutic agents following PTA for the inhibition of restenosis has also been proposed. Therapeutic treatments usually entail pushing or releasing a therapeutic capable agent through a catheter or from a stent. While holding great promise, the delivery of therapeutic agents for the inhibition of restenosis has not been entirely successful.

[08] As an alternative or adjunctive to the above mentioned therapies, the administration of therapeutic agents following PTA for the inhibition of restenosis has also been proposed. Therapeutic treatments usually entail pushing or releasing a drug through a catheter or from a stent. While holding great promise, the delivery of therapeutic agents for the inhibition of restenosis has not been entirely successful.

[09] Accordingly, it would be a significant advance to provide improved devices and methods for reducing, inhibiting, or treating restenosis and hyperplasia which may follow angioplasty and other interventional treatments. This invention satisfies at least some of these and other needs.

[10] Description of the Background Art. Local drug delivery for the prevention of restenosis is described in *Lincoff et al.* (1994) Circulation 90:2070-2084. A full description of an exemplary luminal prosthesis for use in the present invention is described in co-pending application No. 09/565,560 filed May 4, 2000, the full disclosure of which is incorporated herein by reference. Method and apparatus for releasing active substances from implantable and other devices are described in U.S. Patent Nos. 6,096,070; 5,824,049; 5,624,411; 5,609,629; 5,569,463; 5,447,724; and 5,464,650. The use of stents for drug delivery within

[14] As used herein, "susceptible tissue site" refers to a tissue site that is injured, or may become injured as a result of an impairment (e.g., disease, medical condition), or may become injured during or following an interventional procedure such as an intravascular intervention. The term "intravascular intervention" includes a variety of corrective procedures that may be performed to at least partially resolve a stenotic, restenotic, or thrombotic condition in a blood vessel, usually an artery, such as a coronary artery. Usually, the corrective procedure will comprise balloon angioplasty. The corrective procedure may also comprise directional atherectomy, rotational atherectomy, laser angioplasty, stenting, or the like, where the lumen of the treated blood vessel is enlarged to at least partially alleviate a stenotic condition which existed prior to the treatment. The susceptible tissue site may include tissues associated with intracorporeal lumens, organs, or localized tumors. As used herein, the term "intracorporeal body" refers to body lumens or internal corporeal tissues and/or organs, within a corporeal body. The body lumen may be any blood vessel in the patient's vasculature, including veins, arteries, aorta, and particularly including coronary and peripheral arteries, as well as previously implanted grafts, shunts, fistulas, and the like. It will be appreciated that the present invention may also be applied to other body lumens, such as the biliary duct, which are subject to excessive neoplastic cell growth. Examples of internal corporeal tissues and organs, include various organs, nerves, glands, ducts, and the like. In an embodiment, the device includes luminal prostheses such as vascular stents or grafts. In another embodiment, the device may include, cardiac pacemaker leads or lead tips, cardiac defibrillator leads or lead tips, heart valves, sutures, or needles, pacemakers, orthopedic devices, appliances, implants or replacements, or portions of any of the above.

[15] As used herein the term "therapeutic capable agent" includes at least one compound which is either therapeutic as it is introduced to the corporeal body (e.g., human subject) under treatment, or becomes therapeutic after entering the corporeal body of the subject (or exposed to the surface of the corporeal body as the case may be), by for example, reaction with a native or non-native substance or condition. Examples of native conditions include pH (e.g. acidity), chemicals, temperature, salinity, conductivity, contractile or expansive changes of the body lumen/organ, and pulsating nature of the body fluids as they flow through or come in contact with the device; with non-native conditions including those such as magnetic fields, and ultrasound. In the present application, the chemical name of any of the therapeutic capable agents or other compounds is used to refer to the compound itself and to pro-drugs (precursor substances that are converted into an active form of the compound in the body), and/or pharmaceutical derivatives, analogues, or metabolites thereof

implanted within the intracorporeal body. In one embodiment, the structure includes portions having relatively lower and portions having relatively higher mechanical stress or strain profiles with respect to one another. The term "having different mechanical profile" will herein be used to refer to this characteristic of the structure or prosthesis. In an embodiment, when the device may include an axially different coating profile such that the prosthesis comprises a different profile of the therapeutic capable agent and/or the rate-controlling element which will be in the direct flow of the body fluids thus subject to more turbulent flow.

[19] The source may be disposed or formed adjacent at least a portion of the structure. The source may be disposed or formed adjacent at least a portion of either or both surfaces of the expandable structure, within the interior of the structure disposed between the two surfaces, adjacent either or both the edges, or any combination thereof. The association of the therapeutic capable agent with either or both the structure and the rate-controlling element may be continuous or in discrete segments. In one embodiment, the source is disposed or formed adjacent only a portion of the structure and/or the rate-controlling element, preferably, areas having lower mechanical stress profiles.

[20] The expandable structure may be formed of any suitable material such as metals, polymers, or a combination thereof. In one embodiment, the expandable structure may be formed of an at least partially biodegradable material, selected from the group consisting of polymeric material, metallic materials, or combinations thereof. The at least partially biodegradable material, preferably degrades over time. Examples of polymeric material include poly-L-lactic acid, having a delayed degradation to allow for the recovery of the vessel before the structure is degraded. Example of metallic material include metals or alloys degradable in the corporeal body, such as stainless steel. An exemplary stent for use in the present invention is described in co-pending application No. 09/565,560, the full disclosure of which is incorporated herein by reference.

[21] In an embodiment, the device is a stent generally including a cylindrical frame having proximal and distal ends, and tissue and luminal facing surfaces. The device usually further comprises a plurality of radially expansible unit segments including rings. The rings preferably have a serpentine shape. In an embodiment, the unit segments, preferably include segments having different mechanical profiles, as for example may be exhibit as a result of expansion. In an embodiment, some of the rings may be joined with at least one axially adjacent ring through expansion links. The links preferably have a sigmoidal shape, more preferably, an S shape having a relatively smooth profile along its length to minimize or

[25] In a preferred embodiment the rate-controlling element is formed from a nonporous material, usually a nonporous conformal material. Example of suitable non-porous material include, but not limited to: plasma deposited polymers; sputtered, evaporated, electroplated metals and/or alloys; glow discharge coating; polyethylene; polyurethanes; silicone rubber; cellulose; and parylene including parylene C, N, D, F, or combinations thereof, usually parylene C. In an embodiment, the device comprises a layer of another rate-controlling element which is configured to bind, at least partially, with the therapeutic capable agent. In an embodiment Bovine Serum Albumin (BSA) is disposed adjacent the nonporous rate-controlling element (e.g., parylene) such that as the therapeutic capable agent (e.g., mycophenolic acid) diffuses or elutes out of the nonporous rate-controlling element, the therapeutic capable agent binds with the BSA, further delaying or controlling the release of therapeutic capable agent. Other examples of another rate-controlling element capable of binding with the therapeutic capable agent include quarternary ammonium compounds such as polyethylene imine. In one embodiment a hydrogel compound is disposed under either or both the therapeutic capable agent and the rate-controlling element or in the matrix. As body fluids come in contact with the hydrogel compound, the hydrogel compound swells causing a change in the flow or diffusion properties of the therapeutic capable agent through the rate-controlling element, as for example by causing disruptions in the rate-controlling element layer.

[26] As defined herein, "porous material" refers to a polymeric material or structure having an open cell structure. Such material can be classified as macroporous, microporous (e.g., having cell/pore size ranging from about 1 to about 100 microns), or nanoporous (e.g., having cell/pore size in nanometer range and larger than the actual length of the polymer chains making up the polymer). The typical chain length of such porous material ranges from about 2 to about 100 angstroms (A). As used herein, "nonporous material" refers to materials including coatings, which have no pores or have pore size less than the normal free volume of the material. The free volume is associated with the space between molecules in a material accessible to segmental motions. In an embodiment the rate-controlling element has a free volume equal or less than twice the volume of the rate-controlling element molecule.

[27] At the molecular level most, if not all, of the solid and/or nonporous polymers have at least some free volume which allows for chain motion. The dimension of the free volume space is usually in the order of fractions of the molecular chain length, thus the term nonporous. As temperature increases so does the chain motion and the free volume.

molecular weight, polar or non-polar functional groups, electrical charge, steric hindrance groups, hydrophobic, hydrophilic, or amphiphilic moieties. It should be appreciated that the device may comprise a plurality of rate-controlling elements, each having same or different chemical and physical profiles and characteristics, each being present at similar or different locations, and including none, same, or different therapeutic capable agents. In another embodiment, the device may include areas (e.g., distal and proximal ends of the device) having variable thickness of both the source and the rate-controlling element to allow for slower or faster release.

[33] Suitable nondegradable or slow degrading rate-controlling element materials include, but are not limited to, polyurethane, polyethylenes imine, cellulose acetate butyrate, ethylene vinyl alcohol copolymer, silicone, polytetrafluorethylene (PTFE), parylene, parylast, poly (methyl methacrylate butyrate), poly-N-butyl methacrylate, poly (methyl methacrylate), poly 2-hydroxy ethyl methacrylate, poly ethylene glycol methacrylates, poly vinyl chloride, poly(dimethyl siloxane), poly(tetrafluoroethylene), poly (ethylene oxide), poly ethylene vinyl acetate, poly carbonate, poly acrylamide gels, N-vinyl-2-pyrrolidone, maleic anhydride, Nylon, quarternary ammonium compounds including stearyl ammonium chloride and benzyl ammonium chloride, cellulose acetate butyrate (CAB) and the like, including other synthetic or natural polymeric substances; mixtures, copolymers, and combinations thereof. In an embodiment the rate-controlling element is formed from a material selected from the group consisting of silicone, polytetrafluoroethylene, parylast, polyurethane, parylene, cellulose acetate butyrate; mixtures, copolymers and combinations thereof.

[34] Suitable biodegradable rate-controlling element materials include, but are not limited to, poly(lactic acid), poly(glycolic acid) and copolymers, poly dioxanone, poly (ethyl glutamate), poly (hydroxybutyrate), polyhydroxyvalerate and copolymers, polycaprolactone, polyanhydride, poly(ortho esters); poly (iminocarbonates), polyester amides, polyester amines, polycyanoacrylates, polyphosphazenes, copolymers and other aliphatic polyesters, or suitable copolymers thereof including copolymers of poly-L-lactic acid and poly-e-caprolactone; mixtures, copolymers, and combinations thereof. Other examples of suitable material include polymers, as disclosed in US Patent No. 5,610,241 and issued to Lee et al., and incorporated herein by reference in its entirety. Lee discloses graft polymers having a biodegradable backbone and side chains with reactive amino acid groups and/or protected amino acid groups. The graft polymers are obtained from a biodegradable homopolymer or copolymer starting material having carbonyl group and carbon alpha to carbon of the carbonyl group and having H atom on carbon alpha to carbonyl carbon and consisting

rate-controlling element may comprise multiple adjacent layers formed from the same or different material. The therapeutic capable agent may be present adjacent one or more of the rate-controlling element layers. Additionally and/or alternatively, the therapeutic capable agent may form a matrix and/or matrix interface with one or more of the rate-controlling element layers.

[40] The therapeutic capable agent may be selected from a group consisting of immunosuppressants, anti-inflammatories, anti-proliferatives, anti-migratory agents, anti-fibrotic agents, proapoptotics, calcium channel blockers, anti-neoplastics, anti-cancer agents, antibodies, anti-thrombotic agents, anti-platelet agents, IIb/IIIa agents, antiviral agents, and a combination thereof.

[41] Specific examples of therapeutic capable agent include: mycophenolic acid, mycophenolate mofetil, mizoribine, methylprednisolone, dexamethasone, Certican™, rapamycin, Triptolide™, Methotrexate™, Benidipine™, Ascomycin™, Wortmannin™, LY294002, Camptothecin™, Topotecan™, hydroxyurea, Tacrolimus™ (FK 506), cyclophosphamide, cyclosporine, daclizumab, azathioprine, prednisone, Gemcitabine™, cilostazol (Pletal™), tranilast, quercetin, suramin; metabolites, derivatives, and combinations thereof.

[42] In an embodiment, the source of the therapeutic capable agent is a polymeric material including therapeutic capable agent moieties as a structural subunit of the polymer. The therapeutic capable agent moieties are polymerized and associated to one another through suitable linkages (e.g. ethylenic) forming polymeric therapeutic capable agent. Once the polymeric therapeutic capable agent is brought into contact with tissue or fluid such as blood, the polymeric therapeutic capable agent subunits disassociate. Alternatively, the therapeutic capable agent may be released as the polymeric therapeutic capable agent degrades or hydrolyzes, preferably, through surface degradation or hydrolysis, making the therapeutic capable agent available to the susceptible tissue site, preferably over a period of time. Examples of methods and compounds for polymerizing therapeutic capable agents are described in WO 99/12990 Patent Application by Kathryn Uhrich, entitled "Polyanhydrides With Therapeutically Useful Degradation Products," and assigned to Rutgers University, the full disclosure of which is incorporated herein by reference. An example of a therapeutic capable agents and a suitable reaction ingredient unit includes, mycophenolic acid with adipic acid and/or salicylic acid in acid catalyzed esterification reaction; mycophenolic acid with aspirin and/or adipic acid in acid catalyzed esterification reaction, mycophenolic acid with other NSAIDS, and/or adipic acid in acid catalyzed esterification reaction. In an

[47] In an embodiment, the therapeutic capable agent may be released in a time period, as measured from the time of implanting of the device, ranging from about 1 day to about 200 days; from about 1 day to about 45 days; or from about 7 days to about 21 days.

[48] In an embodiment the release rate of the therapeutic capable agent per day may range from about 0.001 micrograms (ug) to about 1000 ug, usually from about 0.001 ug to about 200 ug, normally from about 0.5 ug to about 200 ug, and typically from about 1 ug to about 60 ug.

[49] In one embodiment, the rate-controlling element is configured to have properties, physical and/or chemical properties (e.g., physical dimensions such as thickness and chemical properties such as polymer chemical structure) such that the flux density of the therapeutic capable agent across the rate-controlling element (or through the matrix as the case may be) to the targeted tissue site ranges from about 1.71x10-14 ug/(cm^2s) to about 1.71x10-8 ug/(cm^2s), usually from about 1.71x10-14 ug/(cm^2s) to about 1 3.43x10-9 ug/(cm^2s), normally from about 8.57x10-12 ug/(cm^2s) to about 3.43x10-9 ug/(cm^2s), and typically from about 1.71x10-11 ug/(cm^2s) to about 1.03x10-9 ug/(cm^2s). The desired flex density is affected by the total interfacial area between the therapeutic capable agent and the rate-controlling element, the diffusion coefficient of the therapeutic capable agent across (or through the matrix) the rate-controlling element. Thus, depending on the nature of the drug and the desired therapeutic dosages (e.g., total flux (ug/day)) and the design of the device (e.g., total area of the device including therapeutic capable agent), the various properties (e.g., physical and/or chemical) may be configured to bring about the desired result.

[50] The therapeutic capable agent may be made available at an initial phase and one or more subsequent phases. When the therapeutic capable agent is delivered at different phases, the initial delivery rate will typically be from about 0 to about 99 % of the subsequent release rates, usually from about 0 % to about 90 %, preferably from about 0 % to 75 %. In an embodiment a mammalian tissue concentration of the substance at an initial phase will typically be within a range from about 0.001 nanogram (ng)/mg of tissue to about 100 ug/mg of tissue; from about 1 ng/mg of tissue to about 100 ug/mg of tissue; from about 1 ng/mg of tissue to about 10 ug/mg of tissue. A mammalian tissue concentration of the substance at a subsequent phase will typically be within a range from about 0.001 ng/mg of tissue to about 600 ug/mg of tissue, preferably from about 1 ng/mg of tissue to about 10 ug/mg of tissue.

[51] The rate of delivery during the initial phase will typically range from about 0.001 ng to about 50 ug per day, usually from about 0.1 ug to about 30 ug per day, more preferably, from about 1 ug per day to about 20 ug per day. The rate of delivery at the

[55] Furthermore, a biocompatible (e.g., blood compatible) layer may be formed over the source and/or the most outer layer of the device, to make or enhance the biocompatibility of the device. Suitable biocompatible material for use as the biocompatible layer include, but are not limited to, polyethylene glycol (PEG), polyethylene oxide (PEO), hydrogels, silicone, polyurethanes, heparin coatings.

[56] In an embodiment, the device further includes another compound, such as another therapeutic capable agent, or another compound enabling and/or enhancing either or both the release and efficacy of the therapeutic capable agent. The another therapeutic capable agent may be associated with expandable structure in the same or different manner as the first therapeutic capable agent.

[57] The another therapeutic capable agent may act in synergy with the therapeutic capable agent, in ways such as compensating for the possible reactions and by-products that can be generated by the therapeutic capable agent. By way of example, the therapeutic capable agent may reduce generation of desired endothelial cells, thus by including a suitable another therapeutic capable agent, more endothelialization may be achieved.

[58] The another therapeutic capable agent may comprise at least one compound selected from the group consisting of anti-cancer agents; chemotherapeutic agents; thrombolytics; vasodilators; antimicrobials or antibiotics antimitotics; growth factor antagonists; free radical scavengers; biologic agents; radiotherapeutic agents; radiopaque agents; radiolabelled agents; anti-coagulants such as heparin and its derivatives; anti-angiogenesis therapeutic capable agents such as Thalidomide™; angiogenesis therapeutic capable agents; PDGF-B and/or EGF inhibitors; anti-inflamatories including psoriasis therapeutic capable agents; riboflavin; tiazofurin; zafurin; anti-platelet agents including cyclooxygenase inhibitors such as acetylsalicylic acid, ADP inhibitors such as clopidogrel (e.g., Plavix™) and ticlopdipine (e.g., Ticlid™), phosphodiesterase III inhibitors such as cilostazol (e.g., Pletal™), glycoprotein IIb/IIIa agents such as abciximab (e.g., Rheopro™); eptifibatide (e.g., Integrilin™), and adenosine reuptake inhibitors such as dipyridmoles; healing and/or promoting agents including anti-oxidants, nitrogen oxide donors; antiemetics; antinauseants; derivatives and combinations thereof. The another therapeutic agent may be released prior to, concurrent with, or subsequent to, the therapeutic capable agent, at similar or different rates and phases.

[59] In an embodiment, the another compound comprises, an enabling compound respondable to an external form of energy, or native condition, to affect the release of the therapeutic capable agent. The respondable compound may be associated with the

porous layers will become at least partially porous when exposed to the conditions in the implanted region, typically a blood vessel. Alternatively, the rate controlling member may become disrupted, e.g., crack or form holes, when implanted. Often, a therapeutic capable agent will be present in the rate-controlling element, usually being the same substance as in the source.

BRIEF DESCRIPTION OF THE DRAWINGS

[63] FIGS. 1A through 1C are cross-sectional views of a device embodying features of the present invention and implanted in a body lumen.

[64] FIGS. 2A through 2N are cross-sectional views of various embodiments of the delivery prosthesis of FIGS. 1A-1C taken along line 2-2.

[65] FIG. 3 is a schematic representation of an exemplary stent for use as the device of the present invention.

[66] FIGS. 4A and 4B are schematic representations of an expanded view of a portion of the Stent of FIG. 3 showing areas having different mechanical profiles.

[67] FIGS.5A through and 8D are schematic representations of different embodiments of the stent of FIG. 4A.

[68] FIGS. 9A through 9D is a schematic representation of an embodiment of the stent of FIG. 4A having an aperture in the rate-controlling element.

[69] FIGS. 10A through 10D are schematic representation of different embodiments of methods for making the stent of FIG. 9.

[70] FIGS. 11A and 11B are schematic representations of an embodiment of the stent of FIG. 4A having deliberate disrupted areas.

[71] FIG. 12 is a schematic representation of an embodiment of a method of making the stent of FIG. 4A disposed on a rotating mandrel.

[72] FIGS. 13A through 13D are schematic representation of different embodiments of apparatus and methods for making the stents of FIG. 4A.

[73] FIGS. 14A through 14C are schematic representations of another embodiment of masking apparatus and methods for making the stent of FIG. 4A.

[74] FIGS. 15A and 15B are schematic representations of spray apparatus and methods for making the stent of FIG. 4A.

[75] FIG. 16 is a graphical representation of the release of a therapeutic capable agent over a predetermined time period.

[76] FIGS. 17A, 17B, 18A, 18B, 19A through 19E, 20A, 20B, 21A, and 21B are graphical representations of the performance of various therapeutic capable agents.

[83] The expandable structure may be formed of any suitable material such as metals, polymers, or a combination thereof. In one embodiment, the expandable structure may be formed of an at least partially biodegradable material, selected from the group consisting of polymeric material, metallic materials, or combinations thereof. The at least partially biodegradable material, preferably degrades over time. Examples of polymeric material include poly-L-lactic acid, having a delayed degradation to allow for the recovery of the vessel before the structure is degraded. Example of metallic material include metals or alloys degradable in the corporeal body, such as stainless steel.

[84] The therapeutic capable agent may be selected from a group consisting of immunosuppressants, anti-inflammatories, anti-proliferatives, anti-migratory agents, anti-fibrotic agents, proapoptotics, calcium channel blockers, anti-neoplastics, anti-cancer agents, antibodies, anti-thrombotic agents, anti-platelet agents, IIb/IIIa agents, antiviral agents, and a combination thereof.

[85] Specific examples of therapeutic capable agent include: mycophenolic acid, mycophenolate mofetil, mizoribine, methylprednisolone, dexamethasone, Certican™, rapamycin, Triptolide™, Methotrexate™, Benidipine™, Ascomycin™, Wortmannin™, LY294002, Camptothecin™, Topotecan™, hydroxyurea, Tacrolimus™ (FK 506), cyclophosphamide, cyclosporine, daclizumab, azathioprine, prednisone, Gemcitabine™, cilostazol (Pletal™), tranilast, quercetin, suramin; metabolites, derivatives, and combinations thereof.

[86] In an embodiment, the source of the therapeutic capable agent is a polymeric material including therapeutic capable agent moieties as a structural subunit of the polymer. The therapeutic capable agent moieties are polymerized and associated to one another through suitable linkages (e.g. ethylenic) forming polymeric therapeutic capable agent. Once the polymeric therapeutic capable agent is brought into contact with tissue or fluid such as blood, the polymeric therapeutic capable agent subunits disassociate. Alternatively, the therapeutic capable agent may be released as the polymeric therapeutic capable agent degrades or hydrolyzes, preferably, through surface degradation or hydrolysis, making the therapeutic capable agent available to the susceptible tissue site, preferably over a period of time. Examples of methods and compounds for polymerizing therapeutic capable agents are described in WO 99/12990 Patent Application by Kathryn Uhrich, entitled "Polyanhydrides With Therapeutically Useful Degradation Products," and assigned to Rutgers University, the full disclosure of which is incorporated herein by reference. An example of a therapeutic capable agents and a suitable reaction ingredient unit includes, mycophenolic acid with adipic

comprise a matrix comprising mycophenolic acid and albumin (e.g., Bovine Serum Albumin or BSA). The presence of the matrix material for which the therapeutic capable agent has an affinity for, as for example BSA, reduces the rate of elusion (thus release) of mycophenolic acid to the susceptible tissue site.

[91] The rate-controlling element may be formed of a non-degradable, partially degradable, substantially degradable material, or a combination thereof. The material may be synthetic or natural; non-polymeric, polymeric, ceramic, or metallic; or a combination thereof. The rate-controlling element may have a porous, microporous, nanoporous, or nonporous morphology, or any combinations thereof. Preferably, when the device comprise a porous rate-controlling element, at least one layer of a nonporous rate-controlling element is disposed between the source and the porous rate-controlling element.

[92] In a preferred embodiment the rate-controlling element is formed from a nonporous material, usually a nonporous conformal material. Example of suitable non-porous material include, but not limited to: plasma deposited polymers; sputtered, evaporated, electroplated metals and/or alloys; glow discharge coating; polyethylene; polyurethanes; silicone rubber; cellulose; and parylene including parylene C, N, D, F, or combinations thereof, usually parylene C.

[93] Suitable nondegradable or slow degrading rate-controlling element materials include, but are not limited to, polyurethane, polyethylenes imine, cellulose acetate butyrate, ethylene vinyl alcohol copolymer, silicone, polytetrafluorethylene (PTFE), parylene, parylast, poly (methyl methacrylate butyrate), poly-N-butyl methacrylate, poly (methyl methacrylate), poly 2-hydroxy ethyl methacrylate, poly ethylene glycol methacrylates, poly vinyl chloride, poly(dimethyl siloxane), poly(tetrafluoroethylene), poly (ethylene oxide), poly ethylene vinyl acetate, poly carbonate, poly acrylamide gels, N-vinyl-2-pyrrolidone, maleic anhydride, Nylon, quarternary ammonium compounds including stearyl ammonium chloride and benzyl ammonium chloride, cellulose acetate butyrate (CAB) and the like, including other synthetic or natural polymeric substances; mixtures, copolymers, and combinations thereof. In an embodiment the rate-controlling element is formed from a material selected from the group consisting of silicone, polytetrafluoroethylene, parylast, polyurethane, parylene, cellulose acetate butyrate; mixtures, copolymers and combinations thereof.

[94] Suitable biodegradable rate-controlling element materials include, but are not limited to, poly(lactic acid), poly(glycolic acid) and copolymers, poly dioxanone, poly (ethyl glutamate), poly (hydroxybutyrate), polyhydroxyvalerate and copolymers, polycaprolactone, polyanhydride, poly(ortho esters); poly (iminocarbonates), polyester amides, polyester

therapeutic capable agent at desired release rate. A non-degradable rate-controlling element may release therapeutic capable agent by diffusion.

[99] FIG. 2D illustrates features of an embodiment having the therapeutic capable agent 28 disposed between one of the tissue or luminal facing surfaces of the expandable structure and the rate-controlling element 43.

[100] As shown in FIG. 2E, the source 25 includes the rate-controlling element 43 formed adjacent at least a portion of one of the tissue or luminal facing surfaces of the expandable structure 16 and forming the matrix 40 with the therapeutic capable agent 28. As noted earlier, the therapeutic capable agent 28 may itself act as a rate-controlling element, as for example, when the polymeric therapeutic capable agent forms a matrix.

[101] The matrix may be formed between the rate-controlling element 43 and the expandable structure 16 and forming a matrix interface 46 therebetween and/or between the therapeutic capable agent 28 and the rate-controlling element 43, as shown in FIGS. 2F and 2G. The matrix interface may formed as a result of the physical disposition of the two layers (e.g., rate-controlling element and the therapeutic capable agent. Alternatively and/or additionally, the matrix interface may be formed as a result of chemical reaction between the therapeutic capable agent and a polymer, oligomer, coupling agent, or small molecule. The matrix interface, preferably, further provides controlling of the release of the therapeutic capable agent to the susceptible tissue site.

[102] In an embodiment, features of which are shown in FIG. 2H, the outer most layer of the prosthesis 13 may be formed of the therapeutic capable agent with or without a matrix interface 46 formed between the outer most layer and the other layers. It should be noted, that the therapeutic capable agent 28, although as shown in most figures as discrete particles, may form a smooth layer or a layer of particles, as for example as part of matrix interface 46 as shown in FIG. 2H.

[103] In an alternate embodiment, features of which are shown in FIG. 2I, at least one layer of a second rate-controlling element 49 is formed over the matrix 40, further affecting the release rate of the therapeutic capable agent 28 to the susceptible tissue site. The second rate-controlling element 49 may be of the same or different material than that forming the first rate-controlling element 43.

[104] Now referring now to FIGS. 2J and 2K, the source may comprise, a plurality of compounds, as for example the first therapeutic capable agent 28 and another compound 50 such as another therapeutic capable agent 50 or an enabling compound 61 (FIG. 2N). Each of the plurality of compounds may be in the same or different area of the source. For

implantation to effect release of the therapeutic capable agent 28. The magnetic particles 61 may be formed from magnetic beads and will typically have a size in a range from about 1 nm to about 100 nm. The magnetic source exposes the prosthesis 13 to its magnetic field at an intensity typically in the range from about 0.01T to about 2T, which will activate the magnetic particles 61 and thereby effect release of the therapeutic capable agent from the prosthesis. The another enabling compound may be present in other configurations of prosthesis 13 as described above.

[108] Other suitable external energy sources, which may or may not require another compound or their performance may not be affected by the presence or absence of another compound, include ultrasound, magnetic resonance imaging, magnetic field, radio frequency, temperature change, electromagnetic, x-ray, radiation, heat, gamma, vibration, microwave, or a combination thereof.

[109] By way of example, an ultrasound external energy source may be used having a frequency in a range from 20 kHz to 100 MHz, preferably in a range from 0.1 MHz to 20 MHz, and an intensity level in a range from 0.05 W/cm2 to 10 W/cm2, preferably in a range from 0.5 W/cm2 to 5 W/cm2. The ultrasound energy would be directed at the prosthesis 13 from a distance in a range from 1 mm to 30 cm, preferably in a range from 1 cm to 20 cm. The ultrasound may be continuously applied or pulsed, for a time period in a range from 5 sec to 30 minutes, preferably in a range from 1 minute to 15 minutes. The temperature of the prosthesis 13 during this period will be in a range from 36°C to 48°C. The ultrasound may be used to increase a porosity of the prosthesis 13, thereby allowing release of the therapeutic capable agent 28 from the prosthesis 13. Other sources of energy, for example, heat or vibrational, may also be used to increase the porosity of the prosthesis or a portion thereof, or alter the configuration of the same.

[110] Furthermore, a biocompatible (e.g., blood compatible) layer may be formed over the source and/or the most outer layer of the device, to make or enhance the biocompatibility of the device. Suitable biocompatible material for use as the biocompatible layer include, but are not limited to, polyethylene glycol (PEG), polyethylene oxide (PEO), hydrogels, silicone, polyurethanes, heparin coatings.

[111] The dimensions of the expandable structure will depend on its intended use. Typically, the expandable structure will have a length in a range from about 5 mm to about 100 mm, usually being from about 8 mm to about 50 mm, for vascular applications. The diameter of a cylindrically shaped expandable structure for vascular applications, in a non-expanded configuration, usually ranges from about 0.5 mm to about 10 mm, more usually

may be separated by other non-ring structures. The description of exemplary stent structures are not intended to be exhaustive, and it should be appreciate that other variations of stent designs usable in the present invention are known to those skilled in the art.

[115] Referring back to FIG. 3, the exemplary stent 70 (embodying features of a stent described in more detail in co-pending U.S. Patent Application No. 08/968,319 and assigned to the assignee of the present invention, the disclosure of which in its entirety is incorporated herein by reference) for use in the present invention comprises from 4 to 50 ring segments 73 (with eight being illustrated). Each ring segment 73 is joined to the adjacent ring segment by at least one of sigmoidal links 76. Each ring segment 73 includes a plurality, e.g., six strut/hinge units, and two out of each six hinge/strut structures on each ring segment 73 will be joined by the sigmoidal links 76 to the adjacent ring segment. Stent 70 as shown in FIG. 3 shows the stent 70 is in a collapsed or non-expanded configuration.

[116] The term "radially expandable" as used herein includes segments that can be converted from a small diameter configuration to a radially expanded, usually cylindrical, configuration which is achieved when the expandable structure 16 is implanted at a desired target site. The expandable structure 16 may be minimally resilient, e.g., malleable, thus requiring the application of an internal force to expand and set it at the target site. Typically, the expansive force can be provided by a balloon, such as the balloon of an angioplasty catheter for vascular procedures. The expandable structure 16 preferably provides sigmoidal links between successive unit segments which are particularly useful to enhance flexibility and crimpability of the stent.

[117] Alternatively, the expandable structure 16 can be self-expanding. Structures for use in the devices of the present invention, including the expandable structure 16 (such as self-expanding structures) are provided by utilizing a resilient material, such as a tempered stainless steel, or a superelastic alloy such as a Nitinol™ alloy, and forming the body segment so that it possesses its desired, radially-expanded diameter when it is unconstrained, i.e. released from the radially constraining forces of a sheath. In order to remain anchored in the body lumen, the expandable structure 16 will remain partially constrained by the lumen. The self-expanding expandable structure 16 can be tracked and delivered in its radially constrained configuration, e.g., by placing the expandable structure 16 within a delivery sheath or tube and removing the sheath at the target site.

[118] Now referring back to FIG. 3, and to FIGS. 4A and 4B, the exemplary stent 70 including features of the invention is shown to generally include a cylindrical frame 79 having proximal and distal ends, 82 and 85, tissue and luminal facing surfaces, 88 and 91, a

capable agents with same or different matrix forming material. The source may be present as a layer, a matrix, as part of a matrix interface, on or within the structure, or combinations thereof. The source may be present as a single layer, or a plurality of layers immediately adjacent one another or separated by another layer (such as another source or a rate-controlling element layer).

[121] In an embodiment features of which are shown in FIGS. 7A through 7D, the stent further comprises a rate-controlling element 43 disposed adjacent (as for example, over) at least a portion of the structure. The rate-controlling element may disposed adjacent the structure on at least one of the tissue or luminal facing surfaces (e.g. FIG. 7A) or only those areas of the stent including the source 25 (e.g., FIG. 7B). When the rate-controlling element is disposed only in some but not all of the areas of the structure, the device may advantageously exhibit a relatively higher flexibility as compared to a structure which is completely covered with the rate-controlling element. In an alternate embodiment, the rate-controlling element may be disposed only on those areas of the structure having a relatively higher stress profile. This latter embodiment may be particularly useful when a device with greater overall coating thickness or one having a rate-controlling element applied over the entire structure, is desired. It should be appreciated that although the rate-controlling element as shown in the figures covers the entire perimeter of the structure, the rate-controlling element may cover only portions of the structure on one or both luminal and tissue facing surfaces and/or the ends of the device. Additionally, the rate-controlling element and/or the therapeutic capable agent may have a different thickness at various locations of the structure, as for example, on the sides being in direct flow of the bodily fluids.

[122] In another embodiment features of which are shown in FIGS. 8A through 8D, the device comprises segments with and without therapeutic capable agent with the rate-controlling element 43 disposed adjacent both the segments including the therapeutic capable agent and those which do not. Preferably, the segments including the therapeutic capable agent are disposed adjacent the relatively lower mechanical profile areas with the relatively higher mechanical profile areas not including the therapeutic capable agent. The rate-controlling element comprises portions having different thicknesses.

[123] Preferably, the thickness of the rate-controlling element disposed adjacent those segments of the device including the therapeutic capable agent (source as for example a reservoir) is relatively thinner than the thickness at other segments of the device. This variable rate-controlling element thickness profile provides for lower likelihood of cracking or pinhole formation at the higher stress areas while maintaining a relatively overall thin

[128] In an embodiment such as that shown in FIG. 6A and 6B when the source is not present in the areas having relatively higher mechanical profile, the thickness of the nonporous rate-controlling element layer, preferably, range from about 50 angstroms to 5 microns.

[129] In another embodiment, as shown in FIGS. 9A through 9D, the device may include apertures or orifices 100 in the therapeutic capable agent reservoir, made and used by similar processes as those described below, allowing for controlled release of the therapeutic capable agent to the targeted intracorporeal site.

[130] The apertures 100 may be positioned in the rate-controlling element (e.g., nonporus rate-controlling element such as parylene) either or both directly above and offset from the therapeutic capable agent source, as for example shown in FIGS. 9B and 9C, respectively.

[131] The apertures may have depth running the entire thickness of the rate-controlling element layer or one shorter than the entire depth depending on the desired release rate. A single device may include similar or different apertures, sizes, locations, patterns, and depths in order to effectuate the desired release rate of the therapeutic capable agent. The aperture may range in opening from about 1 angstrom to about 100 microns, usually from about 1 angstrom to about 8 microns.

[132] In an embodiment, as shown in FIG. 9D, the source and the rate-controlling element have at least a portion emerging out of the structure surface. The emerged portion 103 may include an aperture (surface or one having a more substantial depth) allowing for a capillary-like function. The emerged portion, advantageously, will be relatively more in contact with the tissue at the targeted intracorporeal site allowing for more direct release of the therapeutic capable agent to the tissue and less into the blood stream thus minimizing wash out of the therapeutic capable agent.

[133] The amount and type of the therapeutic capable agent in each source (e.g., reservoir) may be the same or different. In an example, to minimize or reduce edge effect, the therapeutic capable agent is present at a greater amount at the ends of the device.

[134] The embodiments including the at least one aperture may particularly be helpful in controllably increase the release rate of the therapeutic capable agent to greater than 2 ug/day, preferably greater than about 5 ug/day, and more preferably greater than about 10 ug/day; where the rate without the apertures may have been less than 50ug/day, preferably less than 5 ug/day, more preferably less than 2 ug/day.

and/or the rate-controlling element layer disposed adjacent (e.g., on the exterior surface of the therapeutic capable agent layer), may crack, disrupt, and/or form pinholes during as the device is expanded or exposed to the targeted intracorporeal site environment. Consequently, the therapeutic capable agent is released at a higher rate in this disrupted areas. As device is aged upon usage, the profile of the rate-controlling element may change (e.g., change in the size of the disrupted area, porosity increase as a result of movement of elution fluid to and from the therapeutic capable agent).

[140] In yet another embodiment, the therapeutic capable agent has a degree of crystallinity less than about 90%, usually less than about 50%. The lower crystallinity may be achieved by heating any of the embodiments of the therapeutic capable agent-coated device (before or after the application of the rate-controlling element) to higher temperature, usually about or greater than the melting point of the therapeutic capable agent, for a period of time sufficient to bring about the desired degree of crystallinity, usually from about 1 minute to about 24 hours, typically from about 30 minutes to about 2 hours. As the therapeutic capable agent melts, it becomes more amorphous, thus less brittle. The amorphous (or semi-amorphous) nature of the therapeutic capable agent reduces creation of pin holes or unwanted interruptions in the rate-controlling element layer, thus a more controlled rate of release.

[141] The heating of the therapeutic capable agent-coated device with or without the rate-controlling element may additionally serve to change, as for example, reduce the residual stress of the device due to the molecular rearrangement of the therapeutic capable agent and/or the rate-controlling element.

[142] In an embodiment, the therapeutic capable agent/rate-controlling element-coated device is heated to a temperature for a period of time sufficient to change, usually reduce the residual stress in the rate-controlling element to about less than 10%, usually to about less than 5%, typically to about less than 1%, normally to about less than 0.5%. Typically, the device is heated to a temperature about or greater than the Tg of the rate-controlling element, usually between the Tg and the melting point of the rate-controlling element. The period of time ranges usually from about 1 minute to about 24 hours, typically from about 30 minutes to about 2 hours.

[143] The residual stress of the coated device due to the rate-controlling element and/or the therapeutic capable agent may be also be reduced by other means such as: heating the device to a temperature below the Tg of the rate-controlling element or the melting point

[147] A bare structure (e.g., prosthesis) or a coated therapeutic capable agent-structure may be placed in vapor deposition chamber or plasma deposited coating chamber. A therapeutic capable agent in solid or liquid form can be placed directly under the structure in a container or dish in the same chamber. The container may be heated to a desired temperature (i.e., the boiling point or sublimation temperature of the therapeutic capable agent), simultaneously or periodically while the rate-controlling element (e.g., parylene) or plasma deposition occurs. Since the chamber is in vacuum, the gaseous therapeutic capable agent will, by line of sight, coat the structure. The dish configuration (round, square, rectangular, depth, cover with holes), the therapeutic capable agent amounts/distribution, presence of a perforated shield/fence, and other factors will control the thickness, distribution, and uniformity of the therapeutic capable agent dispersed or deposited directly or indirectly onto the stent. Alternatively, nano-size deposition techniques may be used to selectively apply the therapeutic capable agent and/or rate-controlling element to or onto the structure.

[148] By way of example, herein is described a more detail process for applying rate-controlling element and/or therapeutic capable agent on or within a structure. A small diameter mandrel 112 or other means is inserted into the stent. The mandrel-stent structure is then placed in the deposition chamber. Preferably, the mandrel-stent structure may be removably affixed on a rotating device inside the chamber to get more consistent coating, as for example shown in FIG. 12. The deposition chamber is sealed. The rate-controlling element material or its precursor (e.g., parylene C, in its dimer form) is loaded into the ambient temperature vaporizer zone through a load door. The door is then sealed. The amount of rate-controlling element or its precursor loaded depends on the desired or required coating thickness, total surface area of the substrate, deposition chamber size, and type of the rate-controlling element (e.g. parylene N, C, D or F). In an exemplary embodiment, the amount of rate-controlling element precursor (e.g., parylene C dimmer) loaded was about 3 grams. The sealed system is then pumped down by a vacuum pump to a steady state base pressure of for example about –4 to about 100 mTorr, usually from about 4 to about 15 mTorr.

[149] Once the system base pressure has been reached, the vaporizer zone is then heated to an appropriate temperature, as for example from about 70 to about 200 °C (e.g., 80°C). The vaporizer heater is cycled on/off by the chamber pressure controller in order to maintain the pressure in the chamber. As the pressure reaches the chamber-pressure set point, the power to the vaporizer heater is reduced to prevent the chamber pressure from

pressure. At this point, the deposition cycle has completed, the system can be brought back to atmospheric pressure and the coated stent removed.

[155] The process parameters for applying parylene (e.g., parylene C) onto a structure, in an exemplary embodiment, were as follows. The parylene process parameters were: vaporization (sublimation) temperature of about 80 °C, pyrolysis temperature of about 650 °C, base pressure (vacuum) of about 15 mTorr or less, pressure (vacuum) set point of about 20 mTorr above base pressure. The therapeutic capable agent evaporation parameters were: dish temperature before evaporation being below boiling point or sublimation temperature, dish temperature during evaporation at or above boiling point or sublimation temperature, base pressure (vacuum) of about 15 mTorr or less, and pressure (Vacuum) set point of about 20 mTorr above base pressure.

[156] In an exemplary embodiment of a method of making the devices of the invention, as shown in FIG. 13A, a mandrel 112 having an outer diameter, preferably, similar to that of the inner diameter of the stent is positioned within the frame of the stent. To better maintain the stent onto the mandrel, the stent may be sufficiently crimped onto the mandrel so as to prevent the stent from slipping off the mandrel. The mandrel, when formed of a solid material or one having a closed exterior surface may optionally serve as a mask to shield the inner surface of the cylindrical frame (i.e., the luminal surface of the stent) during subsequent coating steps.

[157] Optionally, a mandrel having an outer diameter sufficiently smaller than the inner diameter of the stent and/or one being formed of a sufficiently open lattice structure (the pattern preferably designed to prepare the desired coating pattern on the stent) may be used to allow for the coating of the luminal surface of the stent during the coating process.

[158] Optionally, an expansible balloon 115 having a generally cylindrical expanded shape and formed, preferably, from a material such as silicone rubber, polyurethane, nylon, or the like, may be used as the mandrel. The balloon in its expanded configuration, preferably, has an outer diameter, similar to that of the inner diameter of the stent. Use of the balloon as the mandrel allows for easier removal from the stent after the completion of the coating.

[159] As shown in FIG. 13B, the balloon may be formed so as to include a series of longitudinally spaced apart areas of larger diameter (such as a centipede shape). The larger diameter areas are sufficiently spaced apart so as to come in contact with the luminal surface of the stent being of relatively higher mechanical profile, thus masking the relatively higher stress areas during the coating process.

tool may be used to selectively apply the therapeutic capable agent and/or rate-controlling element to or onto the structure.

[165] The stent is then exposed to a source of therapeutic capable agent, as shown in FIGS. 15A through 15B. The therapeutic capable agent 28 is preferably dissolved or mixed in an appropriate solvent(s) and/or matrix, and applied by methods such as spraying. Preferably, the stent is removably fixed to a rotating device so that the stent may be evenly disposed with the source (therapeutic capable agent as dissolved in a solvent and/or matrix material). Preferably, the width of the source application device is sufficiently long so as to apply the source onto the entire length of the stent. The therapeutic capable agent is dissolved in appropriate matrix material and is then, preferably, sprayed onto the stent (masked or otherwise).

[166] Alternatively, the stent may be coated with the source using other techniques such as powder coating while the stent is in a vacuum deposition chamber or plasma deposition/glow discharge chamber, pulse laser assisted deposition technique, vacuum deposition with the therapeutic capable agent being vaporized in the high vacuum chamber and thereafter deposited onto the stent. After the completion of the coating, the masks are removed from the stent. Excess therapeutic capable agent, if necessary or desired, may be removed from the coated stent as described earlier.

[167] The thickness of the therapeutic capable agent and/or the matrix coating may be controlled by the time period of spraying and the speed of rotation of the mandrel. The thickness of the therapeutic capable agent and/or matrix coating is typically in a range from about 1 angstroms (A) to about 50 microns (um), from about 100 angstroms to about 20 microns, usually from about 100 angstroms to about 10 microns, normally from about 5000 angstroms to about 5 microns, and nominally from abut 7500 angstroms to about 2 microns. Once the stent has been coated with the therapeutic capable agent and/or the matrix, the stent may be placed in a vacuum, oven, or vacuum oven to complete the evaporation of the solvent.

[168] A nonporous parylene coating is clear, transparent, and has film-like qualities. It is resistant to solvent and will not swell more than about 3% in film thickness in organic solvents such as alcohol (isopropanol, methanol, ethanol), ketones (acetones and 2,3-pentanedione), aliphatic hydrocarbons (iso-octane), aromatic hydrocarbons (xylene, toluene), chlorinated olefins (trichloroethylene), chlorinated aromatics (chlorobenzene and O-dichlorobenzene), heterocyclic bases (pyridene), and fluorinated solvents

[175] If desired, the nonporous rate-controlling element can be infiltrated with therapeutic capable agent(s) or small non-active molecules by placing the stent, the therapeutic capable agent, and the rate-controlling element (e.g., nonporous rate-controlling element) in one or more solvents that will swell or can transmit into and through the nonporous rate-controlling element, for a period of time, as for example ranging from about 1 second to about 1 week, usually from about 1 hour to about 72 hours, and often from about 2 hours to about 24 hours. The solvent(s) may or may not contain the therapeutic capable agent or non-bioactive molecules that are dissolved in the solvent(s) depending on whether the source of the therapeutic capable agent or non-bioactive molecule is from the therapeutic capable agent reservoir or from an external source or both. The temperature of the solvent(s) during swelling can range from room temperature to elevated temperatures, up to and including the boiling point of the solvent(s).

[176] The stent with the therapeutic capable agent reservoir and nonporous rate-controlling element are heated to a temperature below which the nonporous rate-controlling element will not be damaged or at temperatures below which the therapeutic capable agent will not significantly degraded, for a period of time, usually ranging from about 1 second to about 1 week, often from about 1 hour to about 72 hours, and nominally from about 2 hours to about 24 hours.

[177] The stent with therapeutic capable agent reservoir and nonporous rate-controlling element can come in contact with one or more vaporized solvents, which are preferably organic, for a period of time, usually ranging from about 1 second to about 1 week, often from about 1 hour to about 72 hours, and nominally from about 2 hours to about 24 hours. The coated therapeutic capable agent stent may then be crimped onto a balloon of a PTCA catheter and deployed into the targeted intracorporeal site.

[178] In another embodiment of a method of making, the expandable structure is first pre-treated by silane treatment, such as methacryloxypropyl-trimethoxysilane (A-174) or other silane coupling agents, to minimize the formation of cracks and/or pinholes during the expansion of the device. By way of example, in a method of making the device, the expandable therapeutic capable agent-coated structure is immersed into a solution of methanol: water: silane having a ratio of about 100:100:2 for a period of time, preferably, 15 minutes. The structure is then removed and let dry for about 10 minutes and is then rinsed with IPA. The treated structure is then processed as described above to further include the rate-controlling element. The silane treatment helps promote the adhesion of the rate-controlling element, such as the non-porous parylene, to the structure material, such as

[184] By way of example, porous rate-controlling element may be obtained, such as a porous parylene C layer, using any of the following exemplary methods.

[185] In an embodiment for creating a device having a porous rate-controlling element, such as porous parylene or plasma deposited/glow discharge film, the temperature of deposition may be substantially below the glass transitional temperature of the rate-controlling element material. By way of example, for parylene C as the rate-controlling element, the glass transitional temperature, Tg, is approximately 80 to 100 °C. As the deposition temperature increases, the crystallinity of the film increases. Higher temperatures allow rearrangements and molecular motion possible after the coating is deposited on the surface of the substrate. The polymeric chain becomes more conformationally ordered. As the deposition temperature decreases, the crystallinity of the film decreases, becoming more amorphous. When the temperature is decrease further, from for example, –40 °C to near liquid nitrogen temperatures (-196 °C), the rate-controlling element film becomes increasingly amorphous and porous. It should be noted that the porous films may be changed to a targeted percentage, or usually change to a nonporous morphologyby annealing the thin films at suitable temperatures for a length of time such as 205 °C in Nitrogen gas for about two hours.

[186] In another embodiment for creating a device having a porous rate-controlling element, porous parylene C layer, any one or more combinations of the following parameters may be used: vaporization (sublimation) temperature of about 20 °C to about 200 °C, preferably about 40 °C to about 60 °C; pyrolysis temperature of about 400 °C to about 900 °C, preferably about 500 °C to about 650 °C, and about or greater than 750 °C for porous parylene C; base pressure (vacuum) of about -4 to about 200 mTorr, preferably about 100 mTorr or greater; pressure (vacuum) set point of about 0 to about 200 mTorr above base pressure; stent temperature of about –196 °C to about 0 °C, preferably about -50 °C or lower, more preferably at about -100 °C. By way of example, in an exemplary embodiment for making the porous parylene C rate-controlling element layer at higher base pressure and or pressure set point, the parameters were set as follows: vaporization temperature of 140 °C, pyrolysis temperature of 690 °C, base pressure of 120 mTorr, pressure set point of 135 mTorr, stent temperature at room temperature. By way of example, in an exemplary embodiment for making the porous parylene C rate-controlling element layer at lower pyrolysis temperature and or vaporization temperature, the parameters were set as follows: vaporization temperature of 60 °C, pyrolysis temperature of 650 °C, base pressure at 15 mTorr, pressure set point at 20 mTorr, and stent temperature at room temperature.

commercially by Aldrich Chemicals). The therapeutic capable agent coated stent was loaded on a mandrel rotating at 200 rpm and a spray gun (sold commercially by Binks Manufacturing) used to dispense the copolymer solution in a fine spray onto the coated stent, as the stent rotated for approximately a 10-30 second time period. The stent was then placed in an oven at 25-35°C for up to 24 hours to complete the evaporation of the solvent.

[190] Example 2 - A stainless steel Duraflex stent (3.0 x 18 mm) was laser cut from a SS tube. The surface area of the stent for receiving the therapeutic capable agent was increased by increasing the surface roughness of the stent. The surface area and the volume of the stent can be further increased by creating 10 nm wide by 5 nm deep grooves along the links of the stent strut. The grooves were created in those stent areas experiencing low stress during expansion so as not to compromise the stent radial strength. The drug was loaded onto the stent and in the stent grooves by dipping or spraying the stent in the therapeutic capable agent solution prepared in low surface tension solvent such as isopropyl alcohol, ethanol, or methanol. The stent was then dried with the therapeutic capable agent remaining on the stent surface, and in the grooves which served as a reservoir for the therapeutic capable agent. Parylene was then vacuum deposited on the stent to serve as a rate-controlling barrier. The drug was eluted from the stent over a period of time in the range from 1 day to 45 days.

[191] Example 3 - A therapeutic capable agent was dissolved in methanol, then sprayed onto the stent. The stent was left to dry with the solvent evaporating from the stent leaving the therapeutic capable agent on the stent. A matrix or barrier (silicone, polyurethane, polytetrafluorethylene, parylast, parylene) was sprayed or deposited on the stent covering the therapeutic capable agent. The amount of therapeutic capable agent varied from about 100 micrograms to 2 milligrams, with release rates from 1 day to 45 days.

[192] Example 4 - A matrix solution including the matrix polymer and a therapeutic capable agent was coated onto a stent, as described in Example 2. The stent was then coated or sprayed with a top coat of a rate-controlling barrier (and/or a matrix material without a drug so as to act as a rate-controlling barrier). Alternatively, the therapeutic capable agent may be coated on a stent via a rate-controlling barrier, and then covered with a top coat (another barrier or matrix). Use of topcoats provides further control of release rate, improved biocompatibility, and/or resistance to scratching and cracking upon stent delivery or expansion.

[193] Example 5 – The therapeutic capable agent may be combined with a second therapeutic capable agent (cytotoxic drugs, cytostatic drugs, or psoriasis drugs). One agent is

[197] Example 8 - Two sets of stents, Sets A and B, were coated with 250 and 300 □g of mycophenolic acid, respectively, according to Example 2. Set A was then coated with 1.7 micron of parylene as the rate-controlling barrier. Set B was first coated with mycophenolic acid followed by a subsequent coating of methylprednisolone as the rate-limiting matrix material, and thereafter coated with 1.3 micron of parylene. The coated stents were then subjected to in vitro elution test as described in Example 7, and the amount of mycophenolic acid eluted was measured. As can be seen from the data represented in FIGS. 18A and 18B (corresponding to stent Sets A and B, respectively), both Sets showed a relatively fast linear release of the mycophenolic acid in the initial phase followed by a relatively slower release in the subsequent phase. This may suggest that the more hydrophobic methylprednisolone may act as a rate-controlling element for the more water soluble mycophenolic acid, and can act to control the release rate of mycophenolic acid along with the Parylene coating. This is useful when the diseased area needs a large bolus of the drug initially and then a sustained slower release.

[198] Example 9 - In order to assess the effect of therapeutic capable agents of the present invention on cell cultures, samples of 5 sets of therapeutic capable agents, as listed below, in varying concentrations were prepared and added to different groups of porcine smooth muscle cell cultures according to standard procedures. Set A, B, C, D, and E corresponded to therapeutic capable agent sets: Mycophenolic acid & Dexamethasone; Mycophenolic acid & Triptolide; Wortmannin and Methotrexate; Triptolide; Mycophenolate Mofetil; respectively. The amount of incorporated thymidine for the different samples of varying concentrations (0.003, 0.031, 0.31, 1.6, and 3.1 micromolar) was measured. As can be seen from the data represented in FIGS. 19A-9E (corresponding to Sets A-E, respectively) the IC50 (defined as the concentration at which 50% of the cells are prevented from proliferating) for the various sets occurred at different concentrations. As can further be noted, Mycophenolate Mofetil (reference E) may not be as effective in the absence of a bio-condition (e.g., subject to bodily fluids such as blood).

[199] Example 10 - In another group of therapeutic capable agents, the amount of incorporated thymidine for samples of varying concentrations (0.003, 0.031, 0.31, 1.6, 3.1, 31, and 156 micromolar) was measured. As can be seen from the data represented in FIGS. 20A-10B, and corresponding to Mycophenolic acid and Methylprednisolone, respectively, the IC50 for these therapeutic capable agent was 1.0 micromolar.

[200] Example 11 - In order to assess the effect of various therapeutic capable agents, cell cultures were subjected to some therapeutic capable agents, using methods

having different rate-controlling element thicknesses. The coated stents were place in porcine serum at 37°C. The therapeutic capable agent was eluted from the stents over a period of time and the amount eluted was measured using HPLC. As can be seen from FIG. 22, the elution rate for the stents decreased as the thickness of the rate-controlling element increased.

[204] Example 15 – A number of stainless steel Duraflex™ stents, having dimensions of approximately 3.5 mm x 18 mm were sprayed with about 700 mg of therapeutic capable agent using a solution of 15 mg/ml methylprednisolone in a 70 % acetone : 30% methanol solvent. The stents were dried and the ethanol was evaporated leaving the therapeutic capable agent on the stents surfaces. Parylene C was then vacuum deposited on the stents to serve as a rate-controlling element, at varying thicknesses. One series of the stents having a rate-controlling element layer thickness of about 1.1 micron was then further processed to include apertures, having nominal diameter of about 0.0005 inch, in the rate-controlling element layer similar to embodiment in FIG. 9B, in configurations of: one aperture on every strut, one aperture on every other strut, 3 apertures on every strut, and a controlled disruption on every strut (e.g., FIG. 9C). The coated stents were place in porcine serum at 37°C. The therapeutic capable agent was eluted from the stents over a period of time and the amount eluted was measured using HPLC. As can be seen from FIGS. 23A (with aperture or disruptions) and 23 B (without apertures or disruptions), the amount of therapeutic capable agent eluted increased for both series (with and without apertures) with increase in the elution period, with the eluted amount increasing as the number of the apertures increases.

[205] Example 16 – A series of stainless steel Duraflex™ stents, having dimensions of approximately 3.5 mm x 18 mm were first masked on the higher stress areas of the stents, according to the embodiment described with respect to FIG. 14C with a tape. The stents were then sprayed with 600 ug of therapeutic capable agent using a solution of 15 mg/ml mycophenolic acid as the therapeutic capable agent in a 100 % methanol solvent. The stents were dried and the solvent was evaporated leaving the therapeutic capable agent on the lower stress areas of the stents. The mask was removed and Parylene C was then vacuum deposited on the stents to serve as a rate-controlling element with a nominal thickness of about 1.1 micron. The therapeutic capable agent was eluted from the stents over a period of time. As can be seen from FIG. 24, the stent having been coated with the therapeutic capable agent only on the low stress areas (using masking) elutes at a lower amount than the one coated

WHAT IS CLAIMED IS:

1. A device for intracorporeal use within a patient's body, comprising:

an implantable scaffold;

at least one source of at least one therapeutic capable agent associated with the scaffold and configured to release the therapeutic capable agent within the patient's body at a controlled rate; and

a rate-controlling element layer covering at least a portion of the source and including at least one therapeutic capable agent and providing for an initial relatively more rapid release of the at least one therapeutic capable agent therapeutic from the rate-controlling element layer as well as a sustained, controlled release of the at least one therapeutic capable agent from the source.

2. A device for intracorporeal use within a patient's body, comprising:

an implantable scaffold;

at least one source of at least one therapeutic capable agent associated with the scaffold ; and

a rate-controlling element disposed adjacent at least a portion of the source and being configured to control the release of the therapeutic capable agent in the patient's body at an initial rate and at a subsequent rate relatively slower than the initial rate.

3. A device as in Claim 1 or 2 wherein the rate-controlling element covers the source.

4. A device as in Claim 1 or 2 wherein the rate-controlling element covers only a portion of the source.

5. A device as in Claim 1 or 2 wherein the source comprises a reservoir.

6. A device as in Claim 5 wherein the reservoir is at least partially disposed over the expandable structure.

7. A device as in Claim 1 or 2 wherein the scaffold comprises a tissue facing and a luminal facing surface.

8. A device as in Claim 7 wherein the reservoir is disposed adjacent the luminal facing surface.

19. A device as in Claim 17 wherein the rate-controlling element is formed from a nonporous material.

20. A device as in Claim 18 wherein the rate-controlling element has a variable thickness.

21. A device as in Claim 20 wherein the rate-controlling element has a greater thickness adjacent scaffold regions having relatively higher mechanical profile.

22. A device for intracorporeal use within a patient's body, comprising:
an implantable scaffold;
at least one source of at least one therapeutic capable agent associated with at least a portion of the scaffold and configured to release the therapeutic capable agent within the patient's body; and
a rate-controlling element disposed adjacent at least a portion of the source and including at least one disruption sufficiently large to permit material transport to or from the source.

23. A device as in Claim 22 wherein the at least one disruption is an aperture.

24. A device as in Claim 22 or 23 wherein the at least one disruption is preformed.

25. A device as in Claim 22 or 23 wherein the at least one disruption is formed in the patient's body.

26. A device as in Claim 22 or 23 wherein the transport comprises at least one of transport of native fluids to the source or of the therapeutic capable agent from the source.

27. A device for intracorporeal use within a patient's body, comprising:
an implantable scaffold;
at least one source of at least one therapeutic capable agent associated with at least a portion of the scaffold and configured to release the therapeutic capable agent within the patient's body; and

36. A device as in Claim 35 wherein the rate-controlling element is configured to release the therapeutic capable agent from the source.

37. A device as in any one of Claims 1, 10, 22, or 27 wherein the device comprises a stent.

38. A device as in Claim 37 wherein the stent comprises metallic material.

39. A device as in Claim 37 wherein the stent comprises polymeric material.

40. A device as in Claim 39 wherein the stent comprises a degradable material.

41. A device as in Claim 39 wherein the stent comprises a non-degradable material.

42. A device as in Claim 37 wherein the device is balloon-expandable.

43. A device as in Claim 37 wherein the device is self-expandable.

44. A device as in Claim 37 wherein the source comprises a matrix.

45. A device as in Claim 44 wherein the matrix includes a matrix material.

46. A device as in any one of Claims 1, 10, 22, 27, or 37 wherein the rate-controlling element is formed from a nonporous material.

47. A device as in Claim 46 wherein the porosity of the rate-controlling element changes upon implanting in the patient's body.

48. A device as in Claim 1, 10, 22, 27, or 37 wherein the rate-controlling element is formed from a porous material.

49. A device as in Claim 46 or 47 wherein the rate-controlling element comprises a parylene polymer or copolymer.

50. A device as in Claim 48 wherein the parylene comprises parylene C.

a substance-containing reservoir positioned over at least a portion of a surface of the scaffold; and

a rate-controlling element layer covering at least a portion of the substance-containing reservoir, the rate-controlling element layer having at least one preformed aperture which is sufficiently large to permit the transport of body fluids to the substance-containing reservoir and/or the release of substance from the reservoir.

59. A luminal prosthesis comprising:

a scaffold which is implantable within a body lumen;

a substance-containing reservoir positioned over at least a portion of a surface of the scaffold, and

a rate-controlling element layer covering at least a portion of the substance containing reservoir, the rate-controlling element layer being configured to fracture when stressed by substantially bending, expanding, stretching, or compressing of the scaffold.

60. A luminal prosthesis comprising:

a scaffold which is implantable within a body lumen;

a substance-containing reservoir positioned over at least a portion of a surface of the scaffold; and

a rate-controlling element layer covering at least a portion of the substance containing reservoir, the rate-controlling element layer being configured to swell to permit release of substance from the reservoir when exposed to a luminal environment.

61. A luminal prosthesis comprising:

a scaffold which is implantable within a body lumen;

a substance-containing reservoir positioned over at least a portion of a surface of the scaffold; and

a rate-controlling element positioned over at least a portion of the surface of the scaffold and covering less than all of the substance containing reservoir.

62. A luminal prosthesis as in any of Claims 53 through 61, wherein the luminal prosthesis comprises a metal stent.

63. A luminal prosthesis as in Claim 62, wherein the metal stent is balloon expandable.

76. A luminal prosthesis as in Claim 73, wherein the parylene is nonporous.

77. A device for intracorporeal use within a patient's body, comprising:

an implantable scaffold;

at least one source of at least one therapeutic capable agent having a degree of crystallinity less than about 90 % and associated with the scaffold and configured to release the therapeutic capable agent within the patient's body ; and

a rate-controlling element disposed adjacent at least a portion of the source and being configured to control the release of the therapeutic capable agent to the patient's body.

78. A device as in Claim 77 wherein the therapeutic capable agent has a degree of crystallinity less than about 50 %.

79. A device for intracorporeal use within a patient's body, comprising:

an implantable scaffold;

at least one source of at least one therapeutic capable agent associated with the scaffold and configured to release the therapeutic capable agent at a targeted tissue site within the patient's body; and

a rate-controlling element disposed adjacent at least a portion of the source and being configured to effectuate a therapeutic capable agent flux density of about 1.71x10-14 ug/(cm^2s) to about 1.71x10-8 ug/(cm^2s).

80. A device for as in Claim 79 wherein the flux density ranges from about 1.71x10-14 ug/(cm^2s) to about 3.43x10-9 ug/(cm^2s).

81. A device for as in Claim 79 wherein the flux density ranges from about 8.57x10-12 ug/(cm^2s) to about 3.43x10-9 ug/(cm^2s).

82. A device for as in Claim 79 wherein the flux density ranges from about 1.71x10-11 ug/(cm^2s) to about 1.03x10-9 ug/(cm^2s).

83. A device for intracorporeal use within a patient's body, comprising:

an implantable scaffold;

91. A method as in Claim 87 wherein the changing step comprises heating the structure to a first temperature for a period of time.

92. A method as in Claim 91 wherein the first temperature is less than the melting point of the therapeutic capable agent.

93. A method as in Claim 91 wherein the first temperature is about the same as the melting point of the therapeutic capable agent.

94. A method as in Claim 91 wherein the at least one therapeutic capable agent comprises a plurality of therapeutic capable agents and the first temperature is about the same as the melting point of the therapeutic capable agent with the lowest melting point.

95. A method as in Claim 91 wherein the first temperature is more than the melting point of the therapeutic capable agent.

96. A method as in Claim 91 wherein the at least one therapeutic capable agent comprises a plurality of therapeutic capable agents and the first temperature is more than the melting point of the therapeutic capable agent with the lowest melting point.

97. A method as in Claim 87, 88, 89, 90, 91, 92, 93, or 95 wherein the changing step is performed before the disposing step.

98. A method as in Claim 87, 88, 89, 90, 91, 92, 93, or 95 wherein the changing step is performed after the disposing.

99. A method as in Claim 87 wherein the chaning step comprises heating the structure to a second temperature for a period of time and is performed after the disposing step.

100. A method as in Claim 99 wherein the heating of the structure to a second temperate is performed under vacuum.

101. A method as in Claim 99 wherein the heating of the structure to a second temperate is performed in the absence of oxygen.

102. A method as in Claim 98 wherein the second temperature is less than the glass transition temperature of the rate-controlling element.

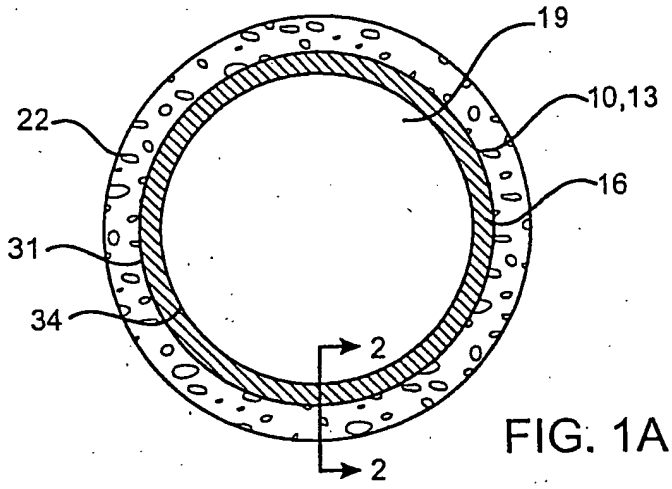


FIG. 1A

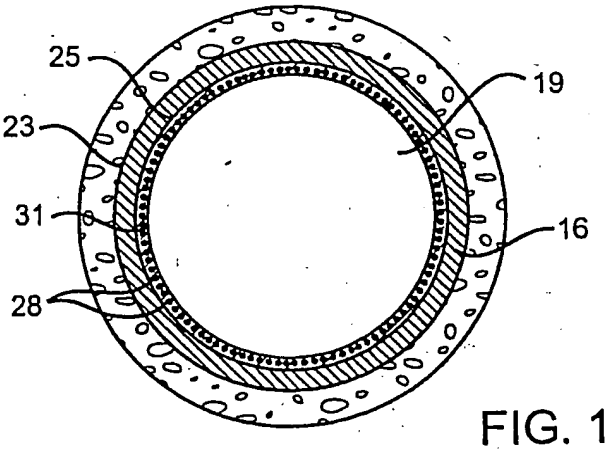


FIG. 1B

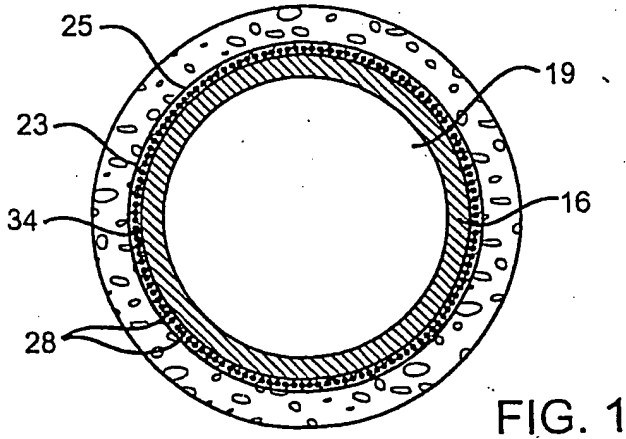


FIG. 1C

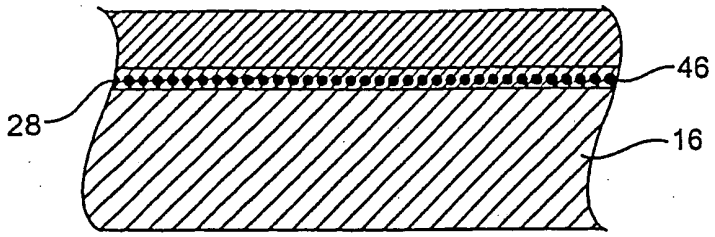


FIG. 2F

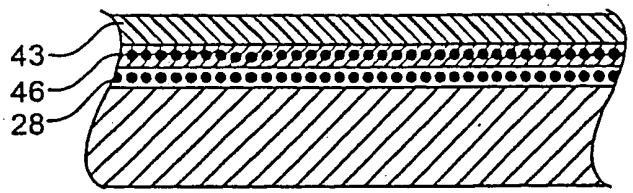


FIG. 2G

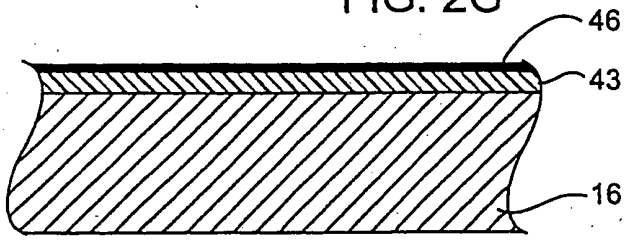


FIG. 2H

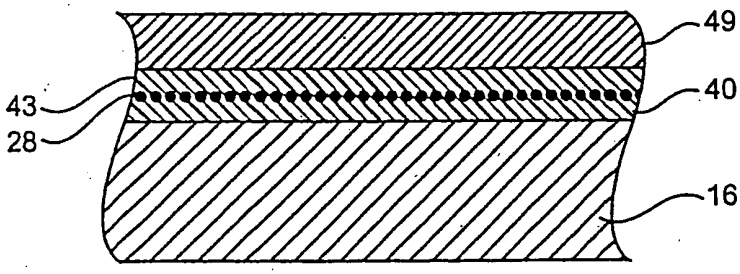


FIG. 2I

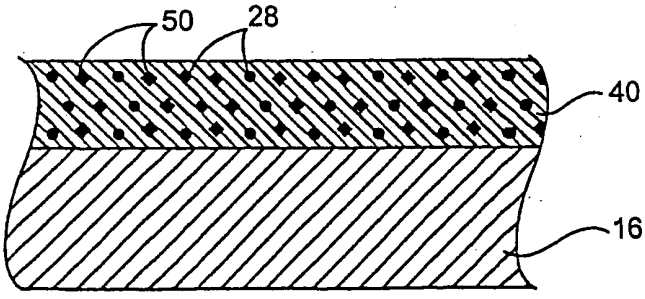


FIG. 2J

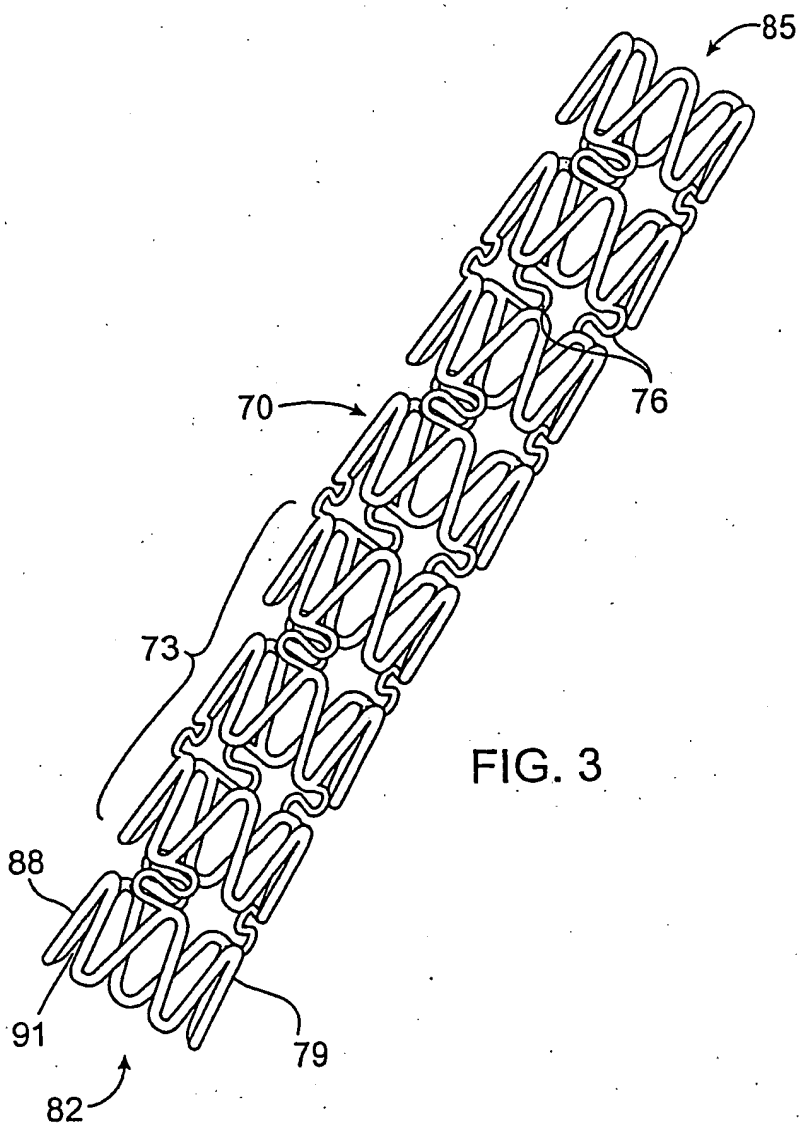


FIG. 3

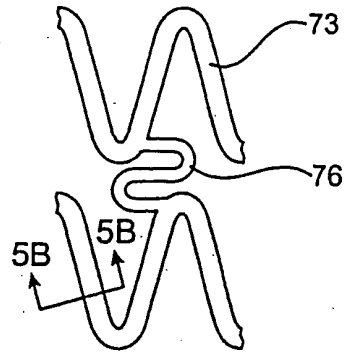


FIG. 5A

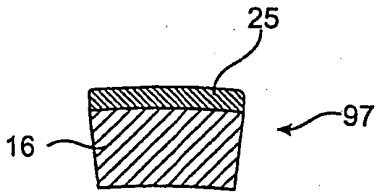
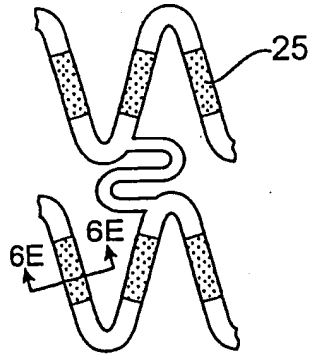


FIG. 5B



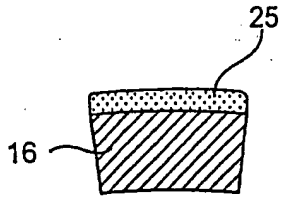
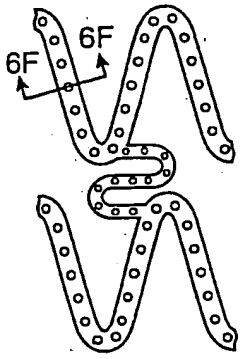


FIG. 6E



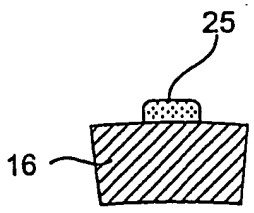
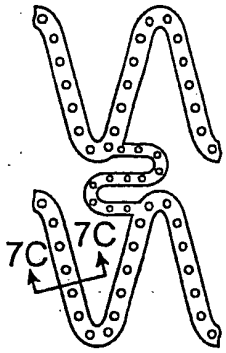


FIG. 6F



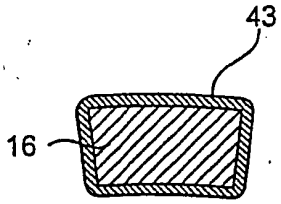
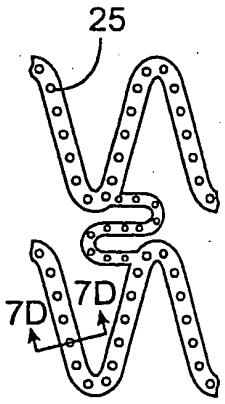


FIG. 7C



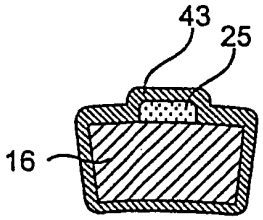
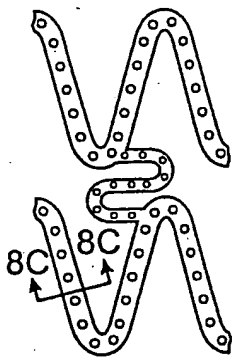


FIG. 7D



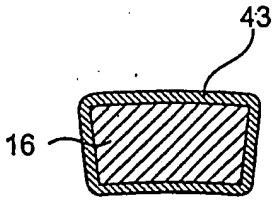
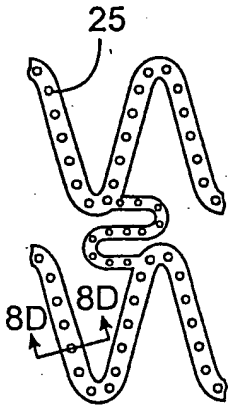


FIG. 8C



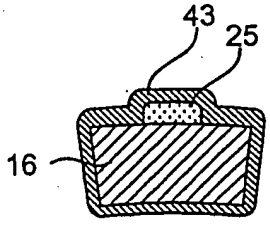


FIG. 8D

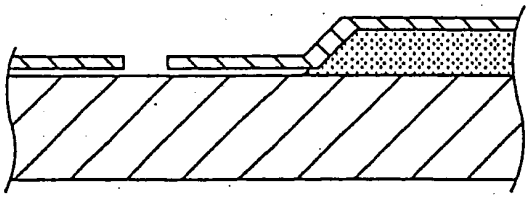


FIG. 9C

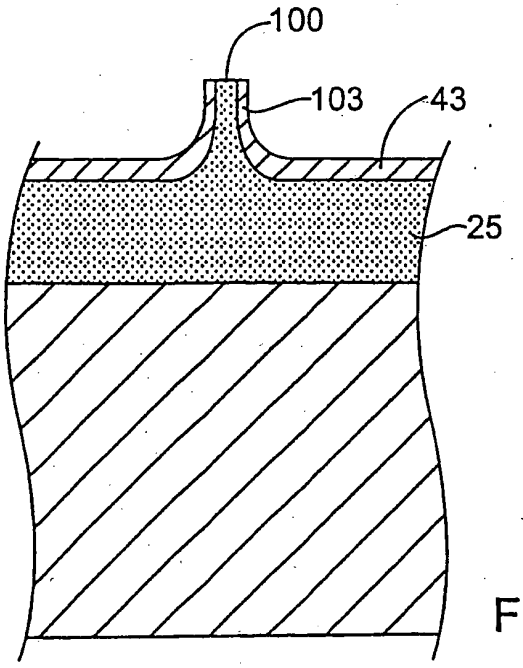


FIG. 9D

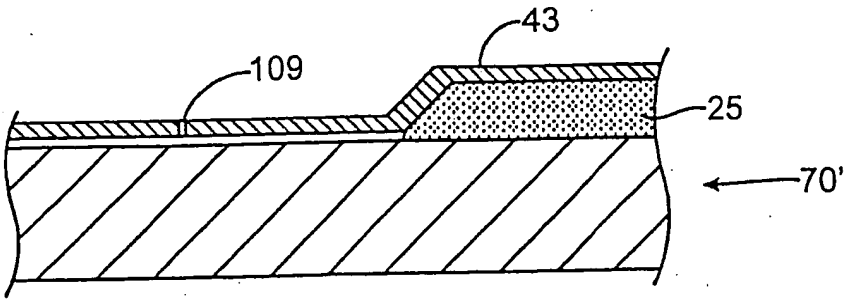


FIG. 11A

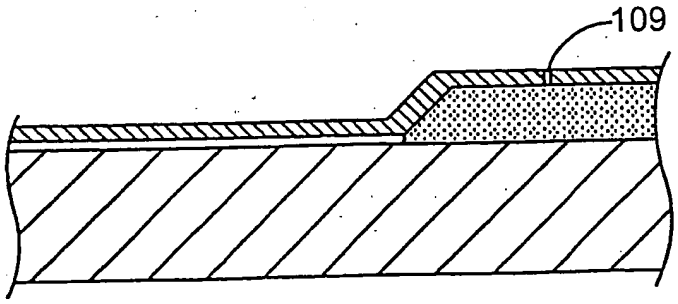


FIG. 11B

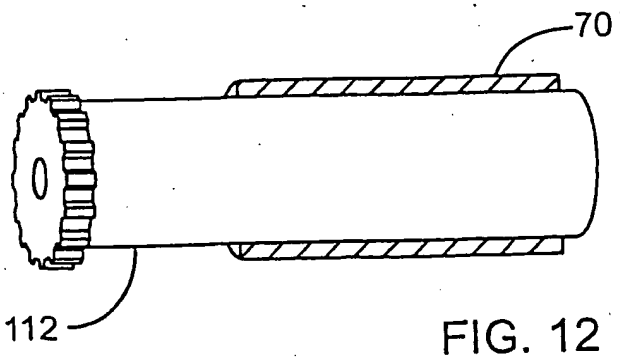


FIG. 12

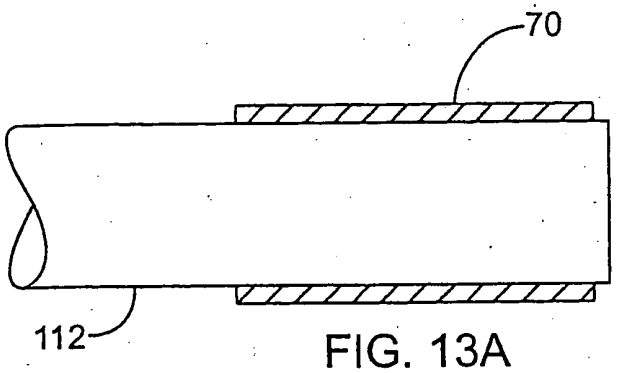


FIG. 13A

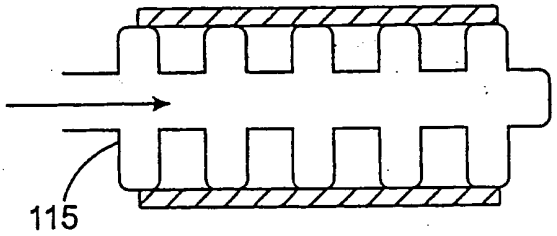


FIG. 13B

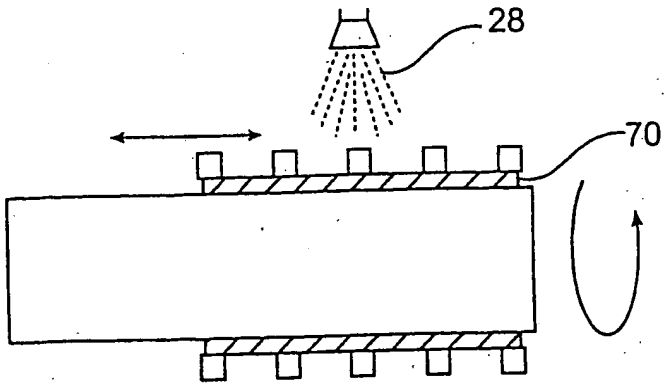


FIG. 15A

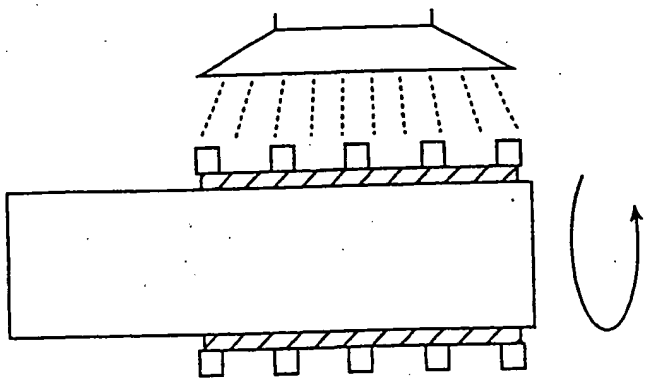


FIG. 15B

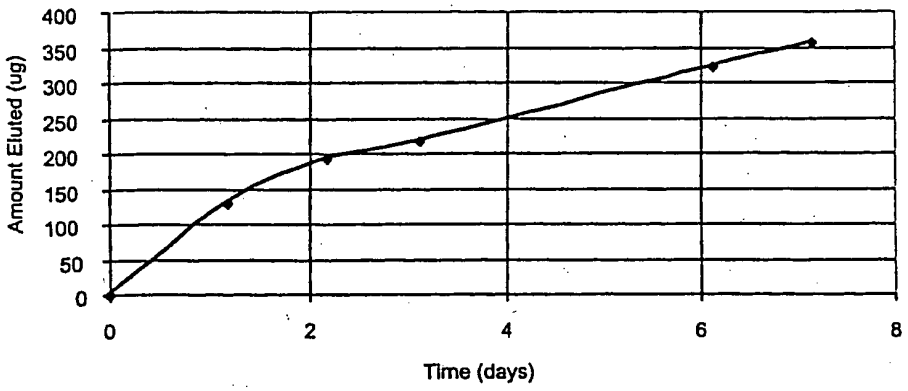


FIG. 17A

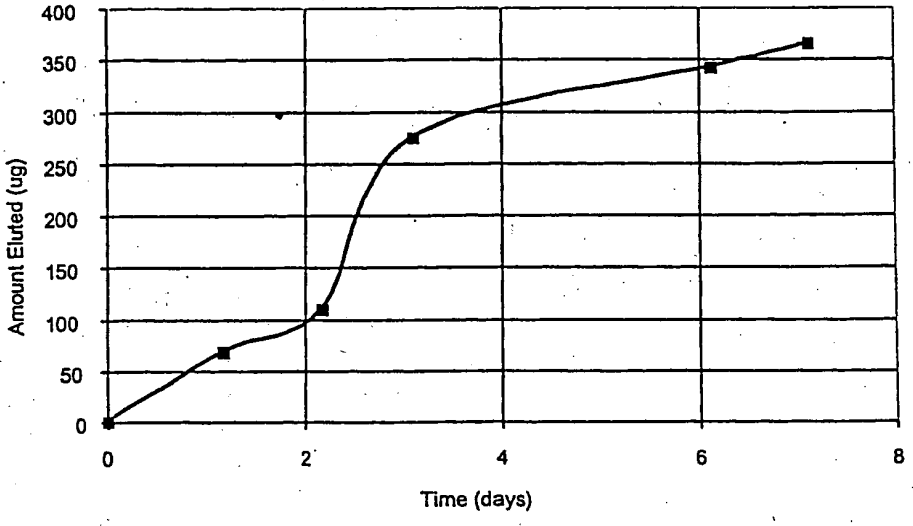


FIG. 17B

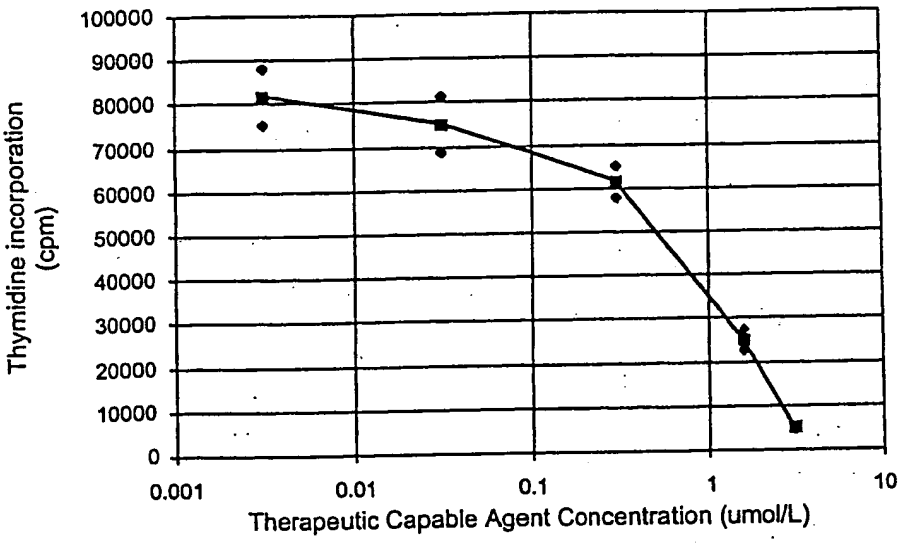


FIG. 19A

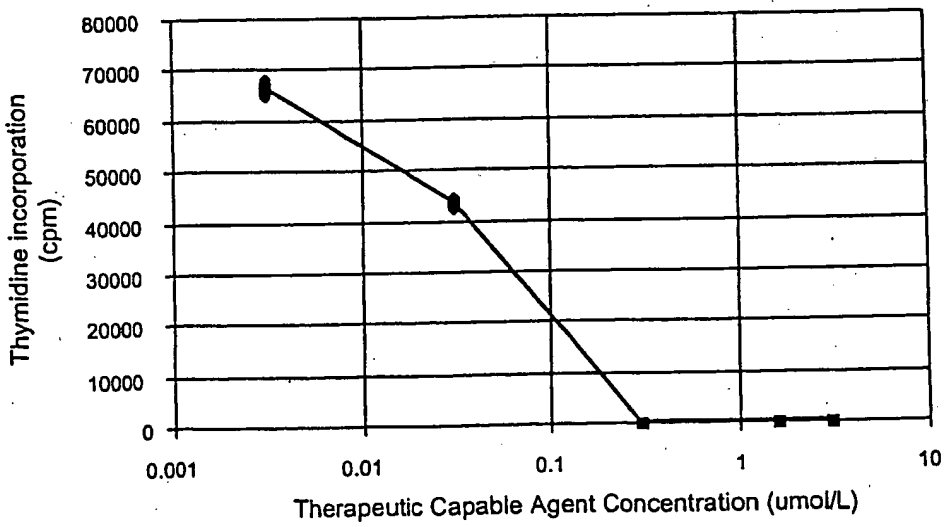


FIG.19B

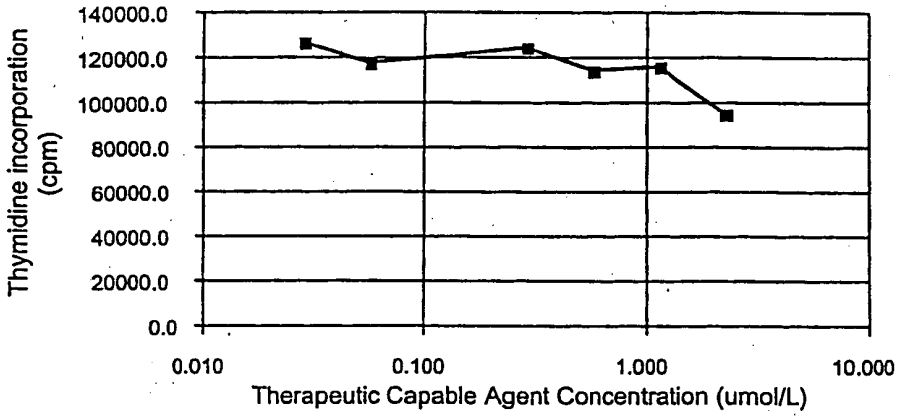

Thymidine incorporation (cpm)
140000.0
120000.0
100000.0
80000.0
60000.0
40000.0
20000.0
0.0
0.010
0.100
1.000
10.000
Therapeutic Capable Agent Concentration (umol/L)

FIG. 19E

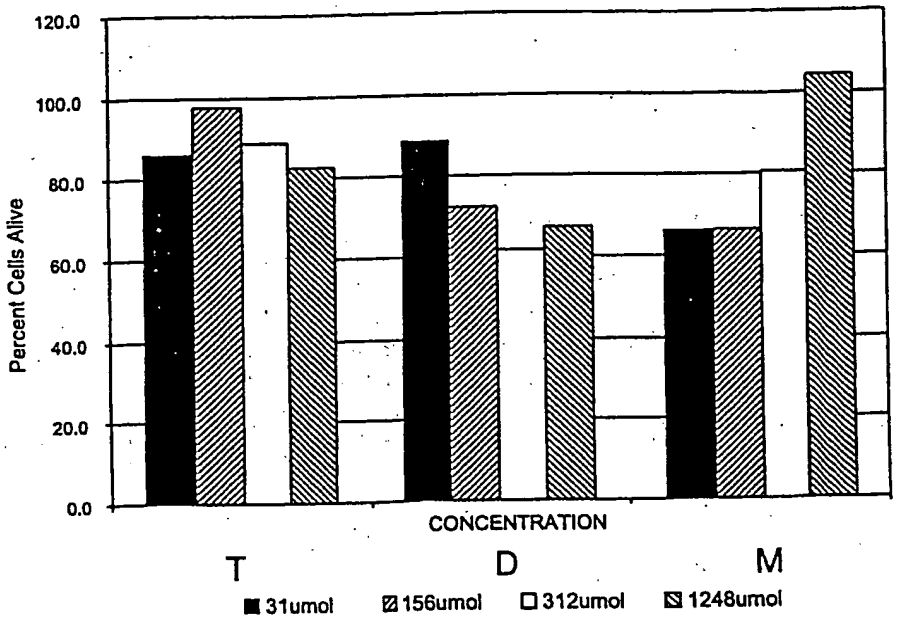

120.0
100.0
80.0
60.0
40.0
20.0
0.0
Percent Cells Alive
CONCENTRATION
T
D
M
31umol
156umol
312umol
1248umol

FIG. 21A

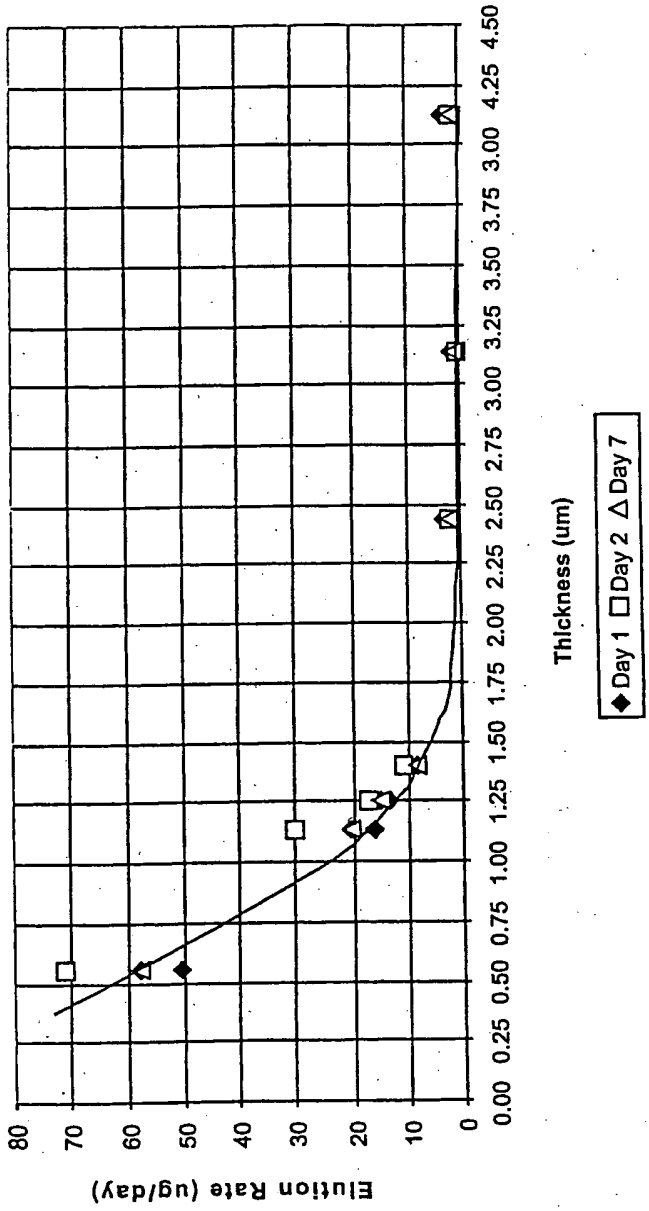

Elution Rate (ug/day)
80
70
60
50
40
30
20
10
0
0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00 2.25 2.50 2.75 3.00 3.25 3.50 3.75 3.00 4.25 4.50
Thickness (um)
Day 1 Day 2 Day 7

FIG. 22

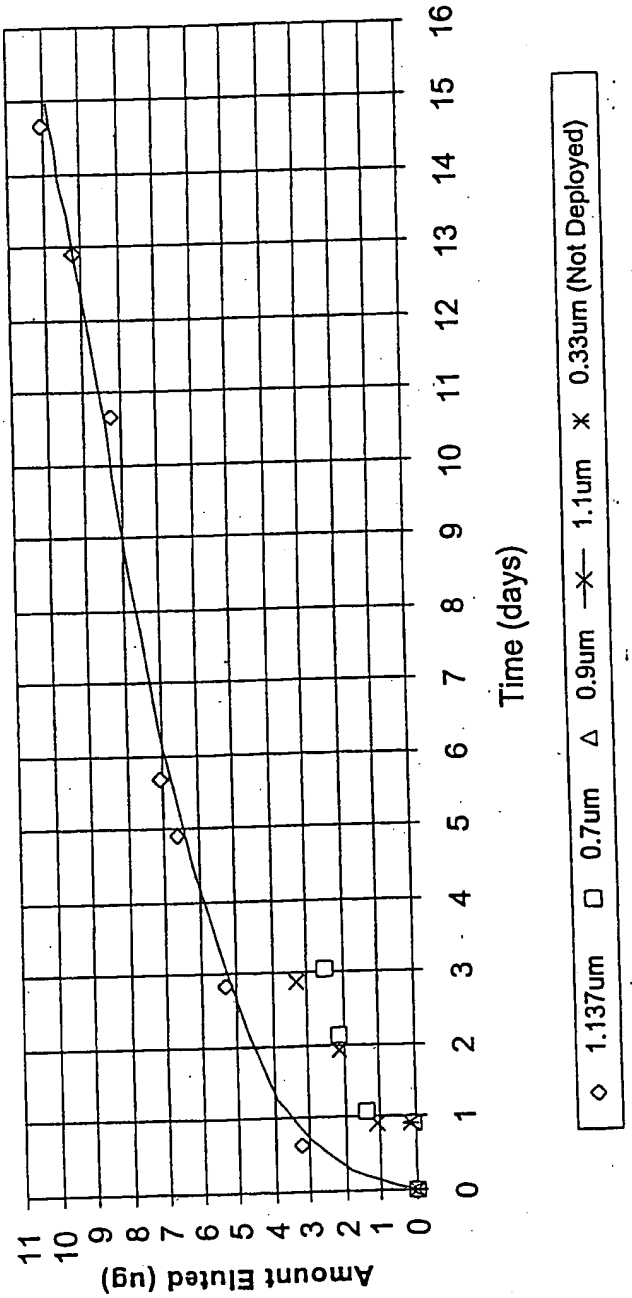

Amount Eluted (ug)
0
1
2
3
4
5
6
7
8
9
10
11
Time (days)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
1.137um
0.7um
0.9um
1.1um
0.33um (Not Deployed)

FIG. 23B

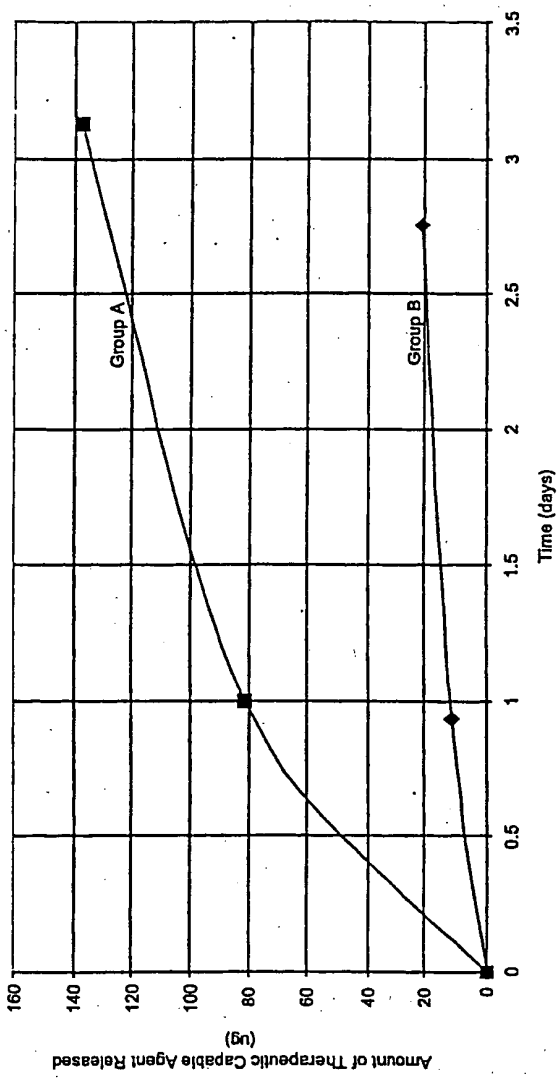

Amount of Therapeutic Capable Agent Released
(ug)
160
140
120
100
80
60
40
20
0
Group A
Group B
0
0.5
1
1.5
2
2.5
3
3.5
Time (days)

FIG. 25